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TENT APPLICATION

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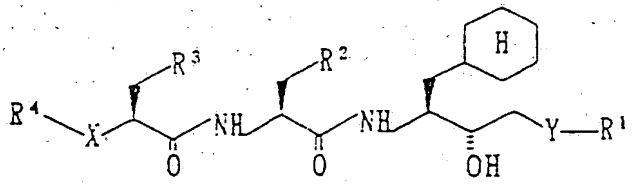
(54) Renin inhibiting dipeptide derivatives, their preparation and pharmaceutical preparations containing them.

(57) A novel dipeptide derivative of the following formula (I), which compound is capable of inhibiting the enzymatic activity of renin and thereby depressing the renin-angiotensin system and lowering the blood pressure, is provided.



(I)

wherein :

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical ;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S- ;

R^3 is aryl or 5- or 6-membered heterocyclic radical ;

R^4 is $R^{4'}$-SO_2 or $R^{4'}$-CO ;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl ; C_3-C_{10} cycloaklyl, or heterocyclic radical ;

X is CH_2, NH, O, or S ; and

Y is CO or $NHSO_2$, wherein R^1, R^2, R^3 and R^4 each may be substituted with one to three substituents selected independently from a group consisting of hydroxy ; halogen ; trifluoromethyl ; -CN ; heterocyclic radical ; C_1-C_6 alkyl ; C_3-C_{10} cycloalkyl ; -O-C_1-C_6 alkyl ; C_1-C_6 alkylenedioxy ; -CO-O-C_1-C_6 alkyl ; -NHCO-C_1-C_6 alkyl ; -S-C_1-C_6 alkyl ; -SO-C_1-C_6 alkyl ; -SO_2-C_1-C_6 alkyl ; -$NHSO_2$-C_1-C_6 alkyl ; -NR^5R^6 ; -O-CO-NR^5R^6 ; -CO-NR^5R^6 ; -O-C_1-C_6 alkyl NR^5R^6 ; R^5 and R^6 are independently hydrogen,

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formyl or C_1-C_6 alkyl, or R^5 and R^6, when taken together with the nitrogen to which they are attached, form a cyclic amino group, or an acid addition salt thereof.

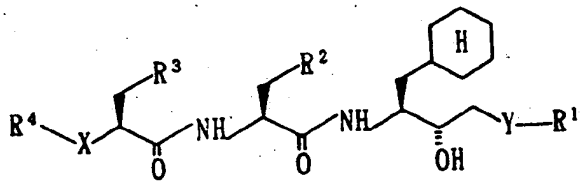
This invention relates to dipeptide derivatives capable of inhibiting renin activity, processes for their production and pharmaceutical preparations comprising them.

Renin (EC3.4.23.15) is a protease which catalyzes the hydrolysis of angiotensinogen into angiotensin I. The angiotensin I is a biologically inactive decap ptide, though it is enzymatically converted into angiotensin II by an angiotensin converting enzyme in pulmonal vascular ndotheliocytes. This system is "the renin-angiotensin system". The angiotensin II induces hypertension through at least two routes, that is, contractive action on smooth muscles of peripheral vasculars and stimulation of secretion of adrenal hormone which inhibits sodium ion excretion. More particularly, it stimulates the secretion of aldosterone, an inhibitor of the excretion of Na^+ ion, resulting in an increase of the volume of extracellular body fluid, rich is one of the causes of hypertension. Accordingly, compounds capable of depressing or inhibiting the renin-angiotensin system are expected to be potent anti-hypertensive substance. Many peptide analogues which seemed to be useful in the regulation of hypertensive diseases on the basis of renin-inhibiting activity have been developed and disclosed [for example, USP 4656269, EP-A-274259 and AU-A-8822959].

As mentioned above, the renin inhibitor inhibits the synthesis of Angiotensin I thereby depressing the renin-angiotensin system and lowering blood pressure. Owing to the physiological activity, renin inhibitors have been used in the treatment of hypertension. However, since hypertension is one of the most common disorders and causes many serious conditions and diseases, a development of more and more novel anti-hypertensive substances including renin inhibitors has been demanded to treat hypertension effectively.

The present inventors have now discovered a class of novel dipeptide compounds capable of inhibiting the catalytic activity of renin both in vitro and in vivo.

In particular, the present invention provides a dipeptide derivative of formula (I):



(I)

wherein:

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S-;

R^3 is aryl or 5- or 6-membered heterocyclic radical;

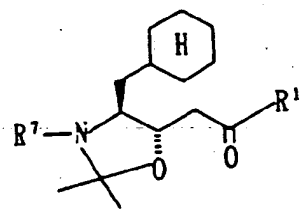
R^4 is $R^{4'}$-SO_2 or $R^{4'}$-CO;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; C_3-C_{10} cycloaklyl, or heterocyclic radical;

X is CH_2, NH, O, or S; and

Y is CO or $NHSO_2$, wherein R^1, R^2, R^3 and $R^{4'}$ each may be substituted with one to three substituents selected independently from a group consisting of hydroxy; halogen; trifluoromethyl; -CN; heterocyclic radical; C_1-C_6 alkyl; C_3-C_{10} cycloalkyl; -O-C_1-C_6 alkyl; -S-C_1-C_6 alkyl; -SO-C_1-C_6 alkyl; -SO_2-C_1-C_6 alkyl; C_1-C_6 alkylenedioxy; -CO-O-C_1-C_6 alkyl; -NHCO-C_1-C_6 alkyl; -$NHSO_2$-C_1-C_6 alkyl; -NR^5R^6; -O-CO-NR^5R^6; -CO-NR^5R^6; -O-C_1-C_6 alkyl NR^5R^6; R^5 and R^6 are independently hydrogen, formyl or C_1-C_6 alkyl, or R^5 and R^6, when taken together with the nitrogen to which they are attached, form a cyclic amino group or an acid addition salt thereof.

In another aspect the present invention also provides a compound of formula (II):



(II)

wherein, R^1 is as defined above, and R^7 is hydrogen or an amino protecting group, which compound is useful as an intermediat for the production of th compound of formula (I).

For the purpose of the present invention, as disclosed and claimed herein, the following terms are defined as below.

The term "C_1-C_{12} alkyl" refers to a straight or branched saturated hydrocarbon radical having one to tw lv carbon atoms, including methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, t-butyl, n-pentyl, isopentyl, 2-methylbutyl, t-pentyl, neopentyl, isopentyl, 1-ethylpropyl, n-hexyl, isohexyl, heptyl, octyl, nonyl, decyl, und - cyl, dodecyl, and the like.

The term "C_1-C_6 alkyl" refers to a straight or branched saturated hydrocarbon radical having one to six carbon atoms as defined above.

The term "C_2 - C_6 alkenyl" refers to a straight or branched unsaturated hydrocarbon radical having two to six carbon atoms and one or more double bonds, including vinyl, allyl, 1-propenyl, isopropenyl, 2-butenyl, 1,3-butadienyl, 2-pentenyl, 1-hexenyl, and the like.

The term "C_2 - C_6 alkynyl" refers to a straight or branched unsaturated hydrocarbon radical having two to six carbon atoms and one or more triple bonds, including ethynyl, 1-propynyl, 2-propynyl, 2-butynyl, 1,3-butadiynyl, 2-pentynyl, 1-hexynyl, and the like.

The term "C_1 - C_6 alkylenedioxy" refers to methylenedioxy, ethylenedioxy, triethylenedioxy, tetramethylenedioxy, pentamethylenedioxy, hexamethylenedioxy, and the like.

The term "C_3 - C_{10} cycloalkyl" refers to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, and the like.

The term "aryl" refers to aryl radicals having 6 to 10 carbon atoms, including phenyl, indenyl, naphthyl, and the like.

The term "halogen" refers to halogen atoms such as fluorine, chlorine, bromine, and iodine.

The term "cyclic amino" refers to monocyclic or bicyclic amino groups such as pyrrolidino, 2-pyrazolidinyl, piperidino, 1-piperazinyl, 1-indolinyl, 2-indolinyl, morpholino, and the like.

The term "heterocyclic group" refers to a group of saturated or unsaturated monocyclic or condensed ring which contains one or more heteroatoms selected from nitrogen, oxygen and sulfur. Examples of heterocyclic groups include, for example, 2-thienyl, 3-thienyl, 2-furyl, 3-furyl, 2-pyrrolyl, 3-pyrrolyl, 2-imidazolyl, 1-pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 3-pyridazinyl, 2-pyrazinyl, 3-triazolyl, 2-thiazolyl, 4-thiazolyl, 5-tetrazolyl, 3-isothiazolyl, 2-pyrrolidinyl, 2-imidazolidinyl, 4-pyrazolidinyl, 4-piperidyl, 2-piperadinyl, 4-indolyl, 7-indolyl, 5-quinolyl, 8-quinolyl, 8-isoquinolyl, and the like.

The term "5- or 6-membered heterocyclic groups" refers to 5- or 6-membered heterocyclic groups as defined above.

The term "carbamoyl" refers to carbamoyl or carbamoyl substituted with one or two substituents selected from a group consisting of C_1 - C_6 alkyl or C_3 - C_{10} cycloalkyl, for example, carbamoyl, methylcarbamoyl, dimethylcarbamoyl, cyclohexylcarbamoyl, and the like.

In the definition of R^1, preferred "C_1-C_{12} alkyl" is methyl, ethyl, propyl, isopropyl, t-butyl, pentyl, hexyl, heptyl, or the like; preferred "C_1-C_6 alkyl" is methyl, ethyl, propyl, isopropyl, t-butyl, or the like; preferred "C_2 - C_6 alkenyl" is vinyl, or the like; preferred "C_2 - C_6 alkynyl" is ethynyl, or the like; preferred "C_3 - C_{10} cycloalkyl" is cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, or the like; preferred "aryl" is phenyl, naphthyl, or the like. Preferred "heterocyclic group" is 5-or 6- membered heterocyclic group such as 2-thienyl, 2-furyl, 2-pyrrolyl, 2-thiazolyl, 4-thiazolyl, 5-tetrazolyl, 4-pyridyl, 5-pyrimidinyl, 2-pyrazinyl, 2-pyrroldinyl, 4-piperidyl, or the like or condensed heterocyclic group such as 8-quinolyl, or the like.

Examples of preferable R^1 include phenyl, o-tolyl, p-tolyl, m-tolyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2,4-dichlorophenyl, 2,6-dichlorophenyl, 2-bromophenyl, 3-bromophenyl, 4-bromophenyl, 2,4-dibromophenyl, 2,6-dibromophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2,4-difluorophenyl, 2,6-difluorophenyl, 2-tolufluoromethyl, 3-tolufluoromethyl, 4-tolufluoromethyl, 2-hydroxyphenyl, 3-hydroxyphenyl, 4-hydroxyphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl, 3,4-methylenedioxyphenyl, 3-methylaminophenyl, 3-(N-formyl)methylaminophenyl, 2-dimethylaminophenyl, 3-dimethylaminophenyl, 4-dimethylaminophenyl, 2-morpholinophenyl, 3-morpholinophenyl, 4-morpholinophenyl, 2-(4-methylpiperazyno)phenyl, 3-(4-methylpiperazyno)phenyl, 4-(4-methylpiperazyno)phenyl, 2-acetamidophenyl, 3-acetamidophenyl, 4-acetamidophenyl, 2-methylsulfonylaminophenyl, 3-methylsulfonylaminophenyl, 4-methylsulfonylaminophenyl, 2-isopropoxycarbonylphenyl, 3-isopropoxycarbonylphenyl, 4-isopropoxycarbonylphenyl, 2-morpholinocarbonylphenyl, 3-morpholinocarbonylphenyl, 4-morpholinocarbonylphenyl, 2-morpholinocarbonyloxyphenyl, 3-morpholinocarbonyloxyphenyl, 4-morpholinocarbonyloxyphenyl, 2-morpholinoethoxyphenyl, 3-morpholinoethoxyphenyl, 4-morpholinoethoxyphenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, naphtyl, 2-pyrrolyl, 3-pyrrolyl, 1-methyl-2-pyrrolyl, 5-tetrazolyl, 1-methyl-5-tetrazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-methyl-4-pyridyl, 2-methyl-4-pyridyl, 3-methyl-4-pyridyl, 1-chloro-4-pyridyl, 2-chloro-4-pyridyl, 3-chloro-4-pyridyl, 1-fluoro-4-pyridyl, 2-fluoro-4-pyridyl, 3-fluoro-4-pyridyl, 2-pyrimidinyl, 5-pyrimidinyl, 2-pyrazinyl, 2-pyrrolidinyl, 3-pyrrolidinyl, 1-methyl-2-pyrrolidinyl, 1-methyl-3-

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(30) Priority : **28.06.90 JP 172050/90**

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(84) Designated Contracting States : **AT BE CH DE DK ES FR GB GR IT LI LU NL SE**

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(74) Representative : **Hardisty, David Robert et al**
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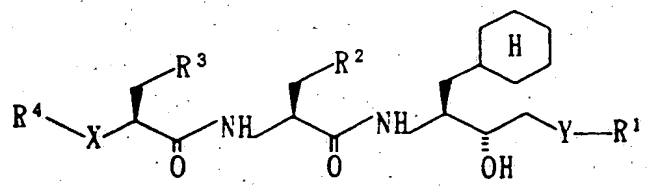

(I)

wherein :

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical ;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S- ;

R^3 is aryl or 5- or 6-membered heterocyclic radical ;

R^4 is $R^{4'}$ -SO_2 or $R^{4'}$ -CO ;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl ; C_3-C_{10} cycloaklyl, or heterocyclic radical ;

X is CH_2, NH, O, or S ; and

Y is CO or $NHSO_2$, wherein R^1, R^2, R^3 and R^4 each may be substituted with one to three substitu nts s lected ind pendently from a group consisting of hydroxy ; halogen ; trifluoromethyl ; -CN ; heterocyclic radical ; C_1-C_6 alkyl ; C_3-C_{10} cycloalkyl ; -O-C_1-C_6 alkyl ; C_1-C_6 alkylenedioxy ; -CO-O-C_1-C_6 alkyl ; -NHCO-C_1-C_6 alkyl ; -S-C_1-C_6 alkyl ; -SO-C_1-C_6 alkyl ; -SO_2-C_1-C_6 alkyl ; -$NHSO_2$-C_1-C_6 alkyl ; -NR^5R^6 ; -O-CO-NR^5R^6 ; -CO-NR^5R^6 ; -O-C_1-C_6 alkyl NR^5R^6 ; R^5 and R^6 are independently hydrogen,

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formyl or C_1-C_6 alkyl, or R^5 and R^6, when taken together with th nitrogen to which they are attached, form a cyclic amino group, or an acid addition salt thereof.

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DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
P,X	EP-A-0 396 065 (YOSHITOMI) 7 November 1990 * example 3 *	1-3,6-7	C07K5/02 C07K5/06 A61K37/64 C07D409/12
P,X	EP-A-0 391 180 (HOFFMANN-LA ROCHE) 10 October 1990 *the whole disclosure, especially scheme 1 on page 13*	4	C07D417/12 C07D401/12 C07D277/56 A61K31/415 C07D233/64
X	EP-A-0 310 015 (HOECHST AG) 5 April 1989 * examples 1,2 *	1-3,6-7	A61K31/425 A61K31/44
X	EP-A-0 264 795 (MERCK PATENT GMBH) 27 April 1988 * the whole document *	1-3,6-7	
X	EP-A-0 155 809 (PFIZER) 25 September 1985 * page 9, line 11 - line 12 *	1-3,6-7	
X	GB-A-2 200 115 (SANDOZ LTD) 27 July 1988 * examples 38-46 *	1-3,5-7	TECHNICAL FIELDS SEARCHED (Int. Cl.5) C07K C07D A61K
X	CHEMICAL ABSTRACTS, vol. 111, no. 1, 3 July 1989, Columbus, Ohio, US; abstract no. 7784c, W J GREENLEE ET AL. 'preparation of peptides containing statine or other peptide bond isosteres of phenylalanylhistidine as renin inhibitors' page 751 ;column RIGHT ; * abstract * & JP-A-63 146 850 (MERCK AND CO.) 18 June 1988	1-3,6-7	

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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 NOVEMBER 1992	p. masturzo

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

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EUROPEAN SEARCH REPORT

Application Number

EP 91 30 5763

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.5)
X	US-A-4 812 442 (BOGER ET AL.) 14 March 1989 * column 27 - column 28 * ---	4	
X	JOURNAL OF POLYMER SCIENCE, POLYMER CHEMISTRY EDITION vol. 23, no. 5, May 1985, NEW YORK US pages 1293 - 1305 K ZHANG ET AL. 'polymeric catalysts. IX. cobalt complexes of polyureas based on bipyridine pyridine and crown ether for aldol condensation' * the whole document * ---	8	
X	CHEMICAL ABSTRACTS, vol. 109, no. 25, 19 December 1988, Columbus, Ohio, US; abstract no. 230725p, A ROSKA ET AL. 'high molecular-weight catalysts in organic synthesis. XVI. catalysis of condensation reaction by polymer-supported crown ethers' page 832 ;column RIGHT ; * abstract * & LATV. PSR. ZINAT. AKAD. VESTIS, KIM. SER. no. 1, 1988, pages 91 - 96 --- -/--	8	TECHNICAL FIELDS SEARCHED (Int. Cl.5)

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	04 NOVEMBER 1992	p. masturzo

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X	CHEMICAL ABSTRACTS, vol. 109, no. 11, 12 September 1988, Columbus, Ohio, US; abstract no. 92416k, I P BELETSKAIA ET AL. 'methylene-carbonyl condensations of some carbon acids with aldehyde under phase-transfer or fluoride-ion catalysis conditions' page 652 ;column LEFT ; * abstract * & ZH. ORG. KHIM. vol. 23, no. 4, 1987, pages 730 - 735	8	

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

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THE HAGUE	04 NOVEMBER 1992	p. masturzo

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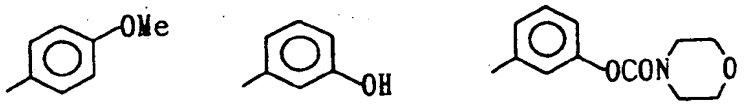
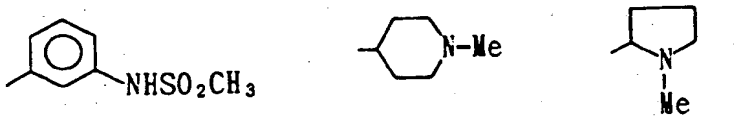
pyrrolidinyl, 2-piperidyl, 3-piperidyl, 4-piperidyl, 1-methyl-2-piperidyl, 1-methyl-3-piperidyl, 1-methyl-4-piperidyl, 8-quinolyl, methyl, ethyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, h xyl, heptyl, octyl, dimethylaminomethyl, morpholinomethyl, 1-morpholinoisopropyl, 1-morpholinoethoxyisopropyl, 1-piperidinomethyl, cyclopropyl, cyclopent ne, cyclohexyl, cycloheptyl, cyclooctyl, 2-morpholinocyclohexyl, 3-morpholinocyclohexyl, 4-morpholinocyclohexyl, 2-m thylaminocycloh xyl, 3-methylaminocyclohexyl, 4-methylaminocyclohexyl, 2-dimethylaminocyclohexyl, 3-dimethylaminocyclohexyl, 4-dimethylaminocyclohexyl, and the like.

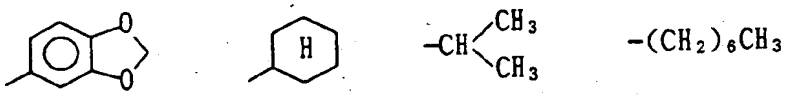
Examples of preferable R^2 include 5-membered heterocyclic groups containing two heteroatoms such as two nitrogen atoms, nitrogen and oxgen atoms, or nitrogen and sulfur atoms, for example, 4-imidazolyl, 4-thiazolyl, 4-oxazolyl, or the like, wherein said heterocyclic group may be substituted with methyl, ethyl, isopropyl, tert-butyl, amine, methylamine, dimethylamine, diethylamine, 1-pyrrolidinyl, piperidino, or the like; C1 - C12 alkyl-S- such as methylthio, ethylthio, cyclohexylthio, or the like; C1-C12 alkyl-S-CH2- such as methylthiomethyl, or the like; carbamoyl or substituted carbamoyl such as methylcarbamoyl, dimethylcarbamoyl, or the like.

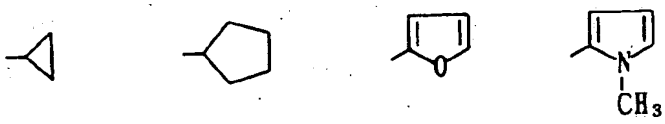
Examples of preferable R^4 include sulfonyl or carbonyl substituted with methyl, ethyl, isopropyl, dimethylamino, tert-butyl, N-morpholino or N-morpholinomethyl, or the like.

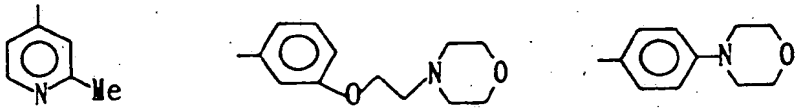
Examples of more preferable R^1 are shown below.

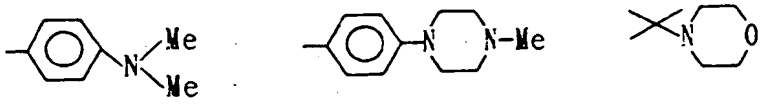


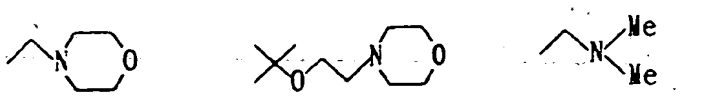


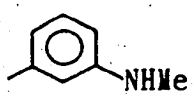








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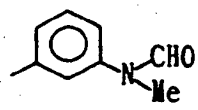
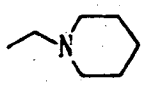

N
CHO
Me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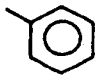

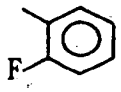
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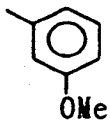
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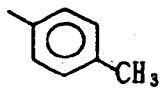
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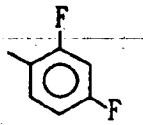
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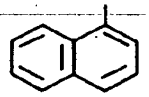
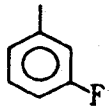



N


S


N
S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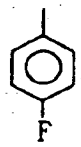
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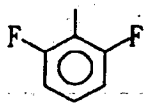
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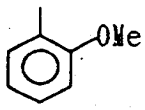
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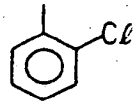
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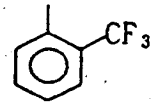
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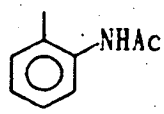
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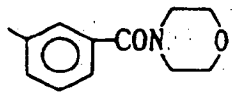
CF3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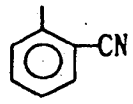
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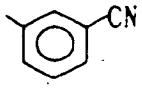
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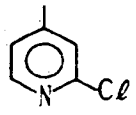
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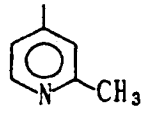
Cℓ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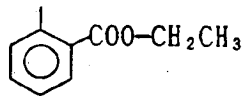
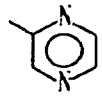

COO–CH2CH3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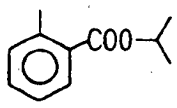
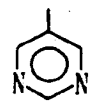
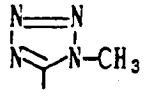
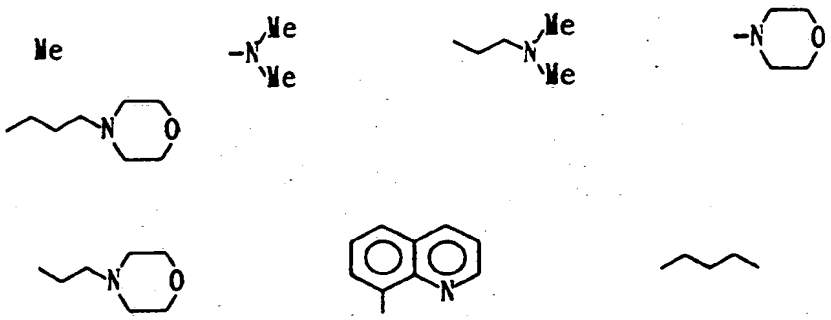
N


COO–


N
N


N
N
N–CH3



Especially preferred compounds are those wherein R^2 is an optionally substituted 5- or 6-membered heterocyclic group; R^3 is an optionally substituted aryl; R^4 is morpholinosulfonyl; and X is NH.

The pharmaceutically acceptable acid addition salts of compounds of formula (I) include salts derived from a mineral acid such as hydrochloric acid, sulfuric acid, p-toluenesulfonic acids, or the like; carboxylic acid such as oxalic acid, maleic acid, citric acid, or the like. Preferable acid addition salts are those derived from mineral acid such as hydrochloric acid, sulfuric acid, toluenesulfonic acid, and the like.

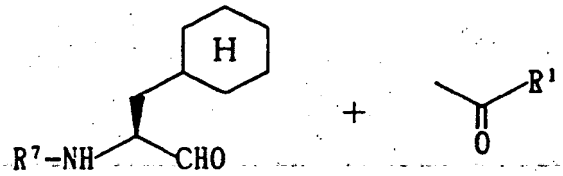
All the compounds of the present invention are novel and can be prepared according to either of two processes described below on the basis of what Y represents.

Process I

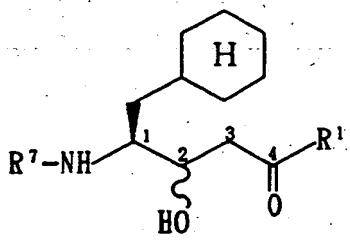
Preparation of compounds wherein Y is CO

The process is schematically shown as below.

Step 1



[1](S) [2]



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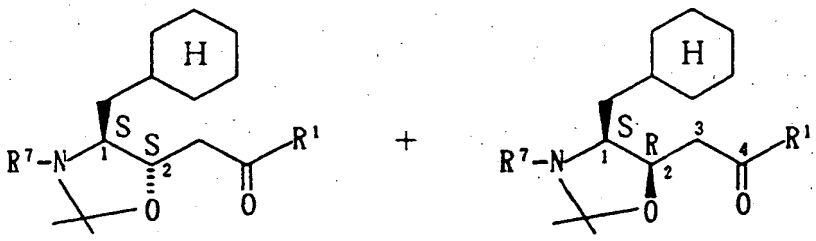
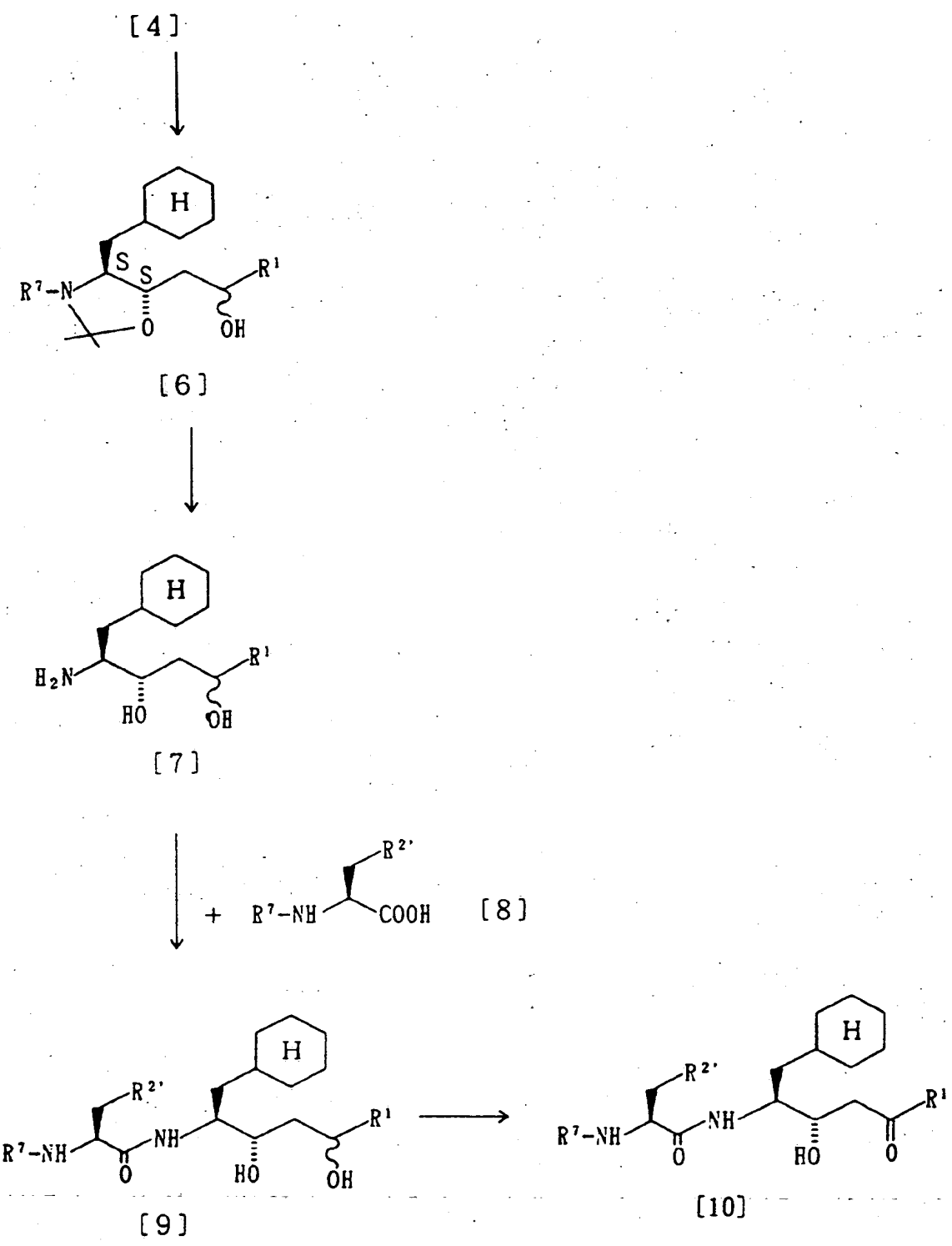
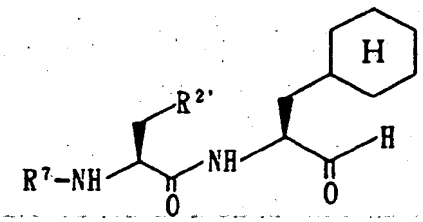


[4] [5]

Step 2a

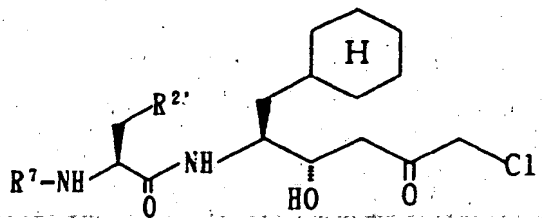

[4]
H
S
S
R7-N
R1
O
OH
[6]
H
H2N
R1
HO
OH
[7]
+
R7-NH
R2'
COOH
[8]
H
R2'
R7-NH
NH
R1
O
HO
OH
[9]
H
R2'
R7-NH
NH
R1
O
HO
O
[10]

Step 2b



[14]

Step 2c



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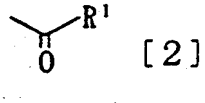

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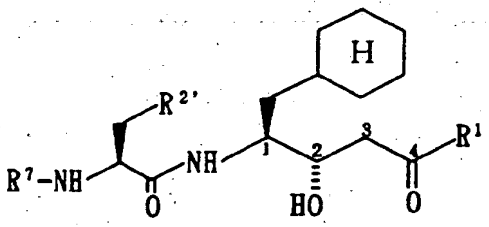
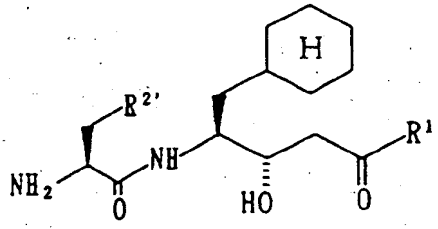


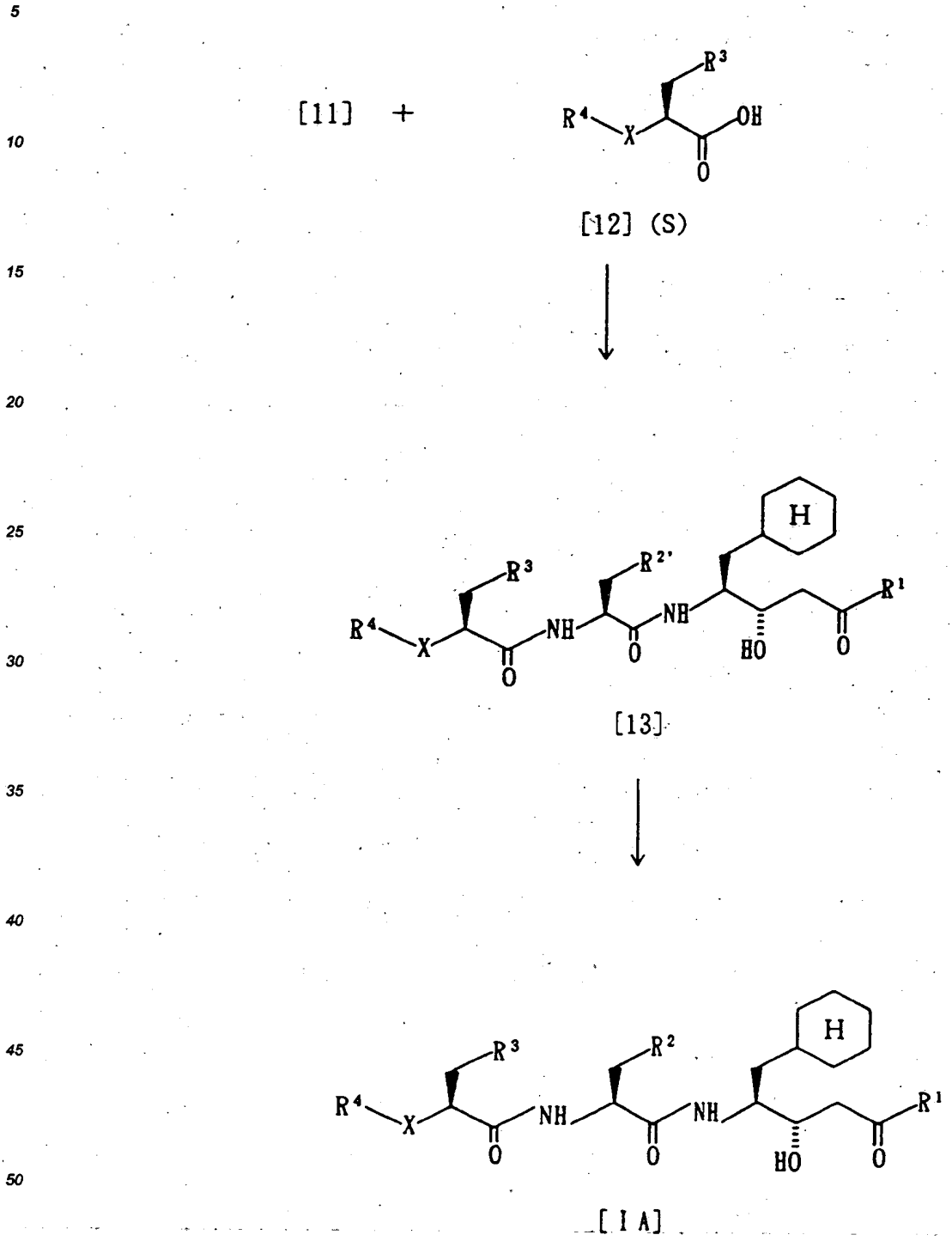
[10]

Step 3



[11]

Step 4



In the above reaction schemes, R^1, R^2 and R^3 are as defined above, $R^{2'}$ is optionally protected R^2 and R^7 is amino-protecting group.

The amino protecting group which is shown by R^7 can be selected from those groups generally used in peptide synthesis. Examples of amino protecting groups include benzyloxycarbonyl (it is referred to as Z), 2,6-dichlorobenzyloxycarbonyl ($Z(Cl)_2$), 4-nitrobenzyloxycarbonyl ($(Z(NO_2)$), 4-methoxybenzyloxycarbonyl

(Z(OMe)), t-butoxycarbonyl (Boc), t-amyloxycarbonyl (Aoc), isobornyloxycarbonyl, adamantyloxycarbonyl (Adoc), 2-(4-biphenyl)-2-propyloxycarbonyl (Bpoc), 9-fluorenylmethoxycarbonyl (Fmoc), methylsulfonylethoxycarbonyl (Msc), trifluoroacetyl, phtalyl, formyl, 2-nitrophenylsulf nyl (NPS), diphenylphosphinothioyl (Ppt), dimethylphosphinothioyl (Mpt), and the like.

Examples of the optionally protected R^2 shown by $R^{2'}$ are 4-imidazoyl, 4-aminothiazolyl and R^2 as defined above, which are optionally protected with a group selected from benzyl (Bzl), benzyloxycarbonyl (Z), toluenesulfonyl (tosyl or Ts), trimethylsilyl (trityl, Trt), dinitrophenyl (Dnp), 2,2,2-trifluoro-1-benzyloxycarbonylaminoethyl (Tfz), 2,2,2-trifluoro-1-t-butoxycarbonyl (TfBoc), adamantyloxycarbonyl (Adoc), piperidinocarbonyl, t-butoxycarbonyl(Boc), and the like.

Step 1

1. Preparation of Compound [3] by Aldol Reaction

a) The optically active aldehyde [1], a required starting compound, can be prepared from, for example, Boc-L-phenylalanine using any of known methods described in literatures such as [1] (T. Shioiri et al., J. Org. Chem. 52:1252 (1987) and J. Boger et al., J. Med. Chem. 28:1779 (1985)).

The aldol condensation between an aldehyde [1] and a ketone [2] is carried out by a novel stereoselective method of the present invention. The reaction is conducted using metal amide, as a base, in an organic solvent in the presence of a crown ether at a temperature of about -78°C. Amides which may be used include sodium bis-trimethylsilylamide ($NaN(TMS)_2$), potassium bis-trimethylsilylamide ($KN(TMS)_2$), lithium diisopropylamide, lithium bis-trimethylsilylamide, and the like. Crown ethers which may be used include 15-crown-5, 12-crown-4, 18-crown-6, and the like. Although all the combinations of amides and crown ethers described above are suited for the stereoselective aldol reaction of the invention, certain combinations are especially preferable in connection with the stereoselectivity of the product [3] which is expressed by the ratio of the product of 2S form to 2R form, i.e., diastereo-selectivity, 2S:2R. Thus, $NaN(TMS)_2$, when used in association with 15-crown-5, gives the most favorable result shown by the 2S:2R value of about 2.4 to about 16.0, while other amides, when used alone or in combination with a crown ether, give inferior results shown by the 2S:2R value of less than 2.

Solvents which may be used include ethers such as diethyl ether, tetrahydrofuran (THF), dimethoxyethane, and the like with a preference for THF. When toluene is used, the stereoselectivity may be relatively decreased.

The reaction is carried out at a temperature ranging from about -20 to about -100°C, preferably about -78°C.

b) Alternatively, the stereoselective aldol condensation reaction can be carried out using metal alkoxide as a base in an inert solvent in the presence of a quarternary ammonium salt at a temperature of about -78°C.

Metal alkoxides which may be used include potassium t-butoxide (t-BuOK), potassium t-amyloxide ($Et(Me)_2COK$) or sodium ethoxide (EtONa), and the like.

Quarternary ammonium salts which may be used include tetrabutyl ammonium bromide ($(n\text{-}Bu)_4NBr$), tetramethyl ammonium bromide ((Me)4NBr), tributylbenzylammonium bromide ($Bn(n\text{-}Bu)_3NBr$), and the like. All the reagents are suited to the stereoselective aldol reaction of the invention and the best result can be obtained by the combination of t-BuOK and $n\text{-}Bu_4NBr$ giving the 3S/3R value of about 3.3 - 6.5. This method is useful even in the absence of quarternary ammonium salt and gives the ratio of 3S/3R of about 3 to 5.

Solvents which may be used include THF, toluene, dichloroethane, dichloromethane, and the like with a preference for dichloromethane. When THF or toluene is used, the stereoselectivity may be decreased. The reaction can be conducted under a similar temperature as described in above a).

2) Separation of Stereoisomer (1S, 2S) [4]

The desired stereoisomer [3]-(2S) can be separated from a mixture of isomers shown by formula [3] by a known resolving procedure, for example, a column chromatography on silica gel. For the purpose of the invention, the desired isomer can be conveniently separated by reacting the mixture [3] with 2-methoxypropene or 2,2-dimethoxypropane in the presence of a catalytic amounts of p-toluene sulfonic acid or pyridinium p-toluene sulfonate in a solvent such as THF or dichloroethane at a temperature ranging from room temperature to the refluxing temperature for about 1 to 8 hours to obtain a product containing a mixture of ring-closed compounds [4] and [5] which differ in the crystallizing properties from a certain solvents. Thus, when the product is recrystallized from ethyl acetate or diisopropyl ether in which the desired stereoisomer [4] is hardly soluble and the undesired isomer [5]-(2R) is soluble, the former can be separated as a crystalline solid, while the latter remains in the mother liquor. A column chromatography on, for example, silica g l, can b us d when the compound [4] is not easily separated by recrystallization. The so obtained compound [4] in (1S, 2S) form is a novel and useful compound as an intermediate for the production of the compound (I).

Alternatively, the product [3], without furth r treatment to form acetonide, can be directly subjected to a column chromatography on silica gel to yield the stereoisomer [3]-(2S), which is then converted into dihydric alcohol of formula [7].

Step 2a

Before the deprotection of C1 amino group, the compound [4] should be reduced to avoid the possibility of ring closing reaction between the deprotected amino group and the C4 carbonyl group. The reducing reaction can be carried out using any of known methods in the art. However, it is efficiently conducted by reacting a solution of the ketone [4] in ethanol, methanol, THF or toluene with a reducing reagent such as sodium borohydrate, L-selectride or Red-Al at room temperature or under cooling for about 0.5 to 2 hours. Preferably, the latter reagent is used slightly in excess, that is, about 1.0 to 1.3 mole to 1.0 mole of ketone [4]. The resultant product [6], a mixture of diastereoisomers (1:1 to 3:1), is used in the next deprotection step without further purification.

The deprotection of amino group can be carried out using any of following procedures. When the protecting group is Boc, and the like, the compound [6] is deprotected by dissolving into THF or dioxane, adding 6N HCl thereto, and stirring at room temperature for about 1 to 4 hours. Alternatively, the compound [6] is treated with an acid such as aluminium chloride, trifluoroacetic acid or formic acid in the presence of anisole to yield the dihydric aminoalcohol [7].

When the protecting group is a member of benzyloxycarbonyl groups such as benzyloxycarbonyl (hereinafter, it is referred to as Z), 2,6-dichlorobenzyloxycarbonyl ($Z(Cl)_2$), or 4-nitrobenzyloxycarbonyl ($(Z(NO_2)$), the deprotection can be effected by catalytic reduction using palladium-containing catalyst, and the like. When the protecting group is Fmoc (9-fluorenylmethoxycarbonyl), Msc (methylsulfonylethoxycarbonyl), or the like, the deprotection can be effected by treating the compound [6] by piperidine, diethylamine, or the like.

The resulting dihydric alcohol of formula [7] is subjected to the next condensation reaction without purification. The condensation can be carried out using any procedure generally used in the field of peptide synthesis. For example, to a solution of compound [7] in an appropriate solvent such as dichloromethane is added commercially available N-Boc-amino acid [8] or its DCHA salt, and the mixture is allowed to react at room temperature for about 1 to 4 hours in the presence of a slight excess of a coupling reagent such as 1.0 to 1.3 mole equivalent of diethyl cyanophosphophosphate (DEPC) and, if desired, a tertiary amine such as N-methyl morpholine to obtain a coupled compound [9]. Examples of coupling reagents are DCC, EDC, DEPA, BOP, DCC-HOBt, DCC-HOSu, ethyl chlorocarbonate, isobutyl chlorocarbonate, isopropyl chlorocarbonate, diethyl chlorophosphate, diphenyl chlorophosphate, 2-chloro-4,6-dimethoxy-1,3,5-triazine, and the like. The compound [8] may be protected at the heterocyclic ring with a protecting group generally used in the field of peptide synthesis.

The resultant diastereisomer [9] is also converted into the corresponding ketone [10] without separation by dissolving the compound [9] into dichloromethane or DMF, adding about 3 to 10 times amounts of active manganese dioxide to the mixture and reacting at room temperature for 2 to 8 hours. This reaction proceeds very smoothly when fine crystal starting material [9] is used. The characteristic of this reaction is that the hydroxyl group at the C4 position of benzyl compound can be selectively oxidized.

Step 2b

Compound [10] can be also prepared through an aldol reaction according to a procedure described in step 1 from a starting compound [2] and a dipeptide aldehyde of formula [14] obtainable from a corresponding dipeptide alcohol in the same manner as that used for the preparation of compound [1]. The reaction however proceeds without stereoselectivity and differs from that of step 1 in this regard. The product being a 1:1 mixture of compound [10] in 2S and 2R isomers, chromatographic procedure is required for the separation of desired [10]-(2S)-isomer. The characteristic of the method of step 2b is that it is applicable when the method of above step 2a is not effective because a compound resists the selective oxidization with manganese dioxide.

Step 2c

The compound [10] can be prepared by reacting a chloromethyl ketone of formula [19] with an amine. The characteristic of the method of step 2c is that it is useful in the introduction of N-substituted methylketone residue to the C-terminal moiety.

Step 3

The deprotection of ketone compound [10] can be carri d out in the same manner as described in the preparation of amino dihydric alcohol [7] from compound [6]. For example, when the protecting group is Boc, it is carried out by adding excess aluminium chloride to an anisole solution of compound [10] and stirring the mixture for about 1 to 3 hours at a temperature ranging from ice-cooled temperature to room temperature. The deprotection can also be effected by treating the compound [10] with either of excess trifluoroacetic acid in anisole or 6N HCl in THF to yield the desired compound [11]. The resultant ketone [11] with carbonyl group at the C4 position is novel and important as an intermediate for preparing the compound of formula (I) of the present invention.

Step 4

The compound [11] is reacted with sulfonyl propionic acid derivatives, N-sulfamyl, N-carbamoyl, or N-acyl amino acid of formula [12] which can be prepared according to a known method such as described in a literature (J.L.Stanton et al., J.Med.Chem. 31:1839 (1988)) under a condition for the coupling reaction and then deprotected if necessary to give the desired compound (IA) as the final product.

The coupling reaction is preferably conducted using 1.0 to 1.3 mole equivalent of diethyl cyanophosphonate (DEPC) in the presence of N-methyl morpholine (NMM) in a solvent such as dichloromethane at room temperature for about 1 to 8 hours. Examples of coupling reagents are DCC, EDC, DEPA, BOP, DCC-HOBt, ethyl chlorocarbonate, isobutyl chlorocarbonate, isopropyl chlorocarbonate, diethyl chlorophosphate, diphenyl chlorophosphate, 2-chloro-4,6-dimethoxy-1,3,5-triazine, and the like.

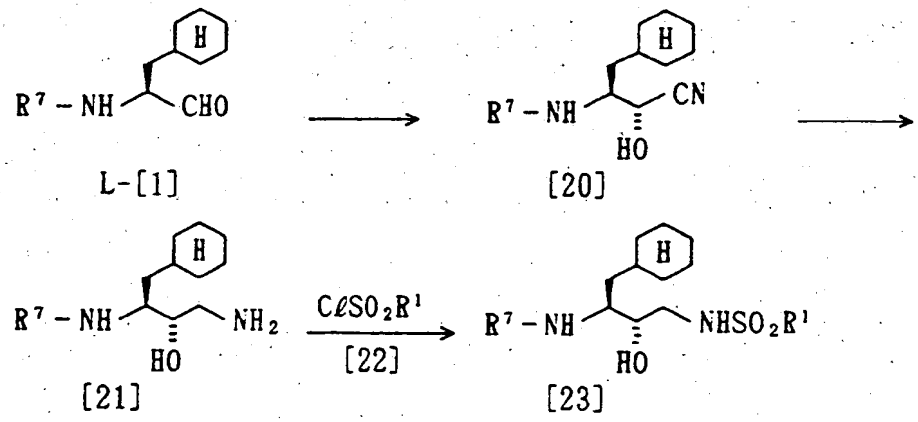
The deprotection of the compound [13] is carried out using any of known procedures depending on the protecting group. When the protecting group of $R^{2'}$ is tosyl, it can be carried out by stirring a mixture of a solution of compound [13] in DMF in the presence of 5 to 12 mole equivalent of pyridinium hydrochloride at room temperature for about 1 to 4 hours. The deprotection can be effected by means of trifluoroacetic acid (at 15°C for about 30 minutes), HBr/acetic acid (at room temperature for about 30 minutes), conc.ammonia (at room temperature for about 1 hour), conc.HCl, or the like.

Process II

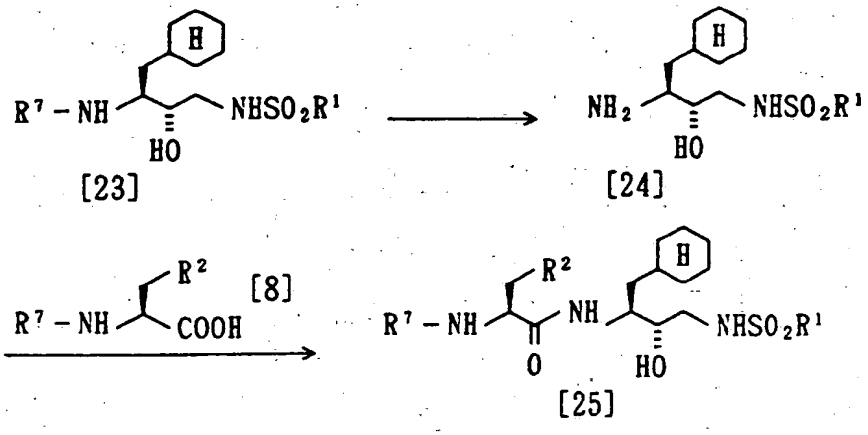
Preparation of compounds (I) wherein Y is $NHSO_2$

The process is schematically shown as below.

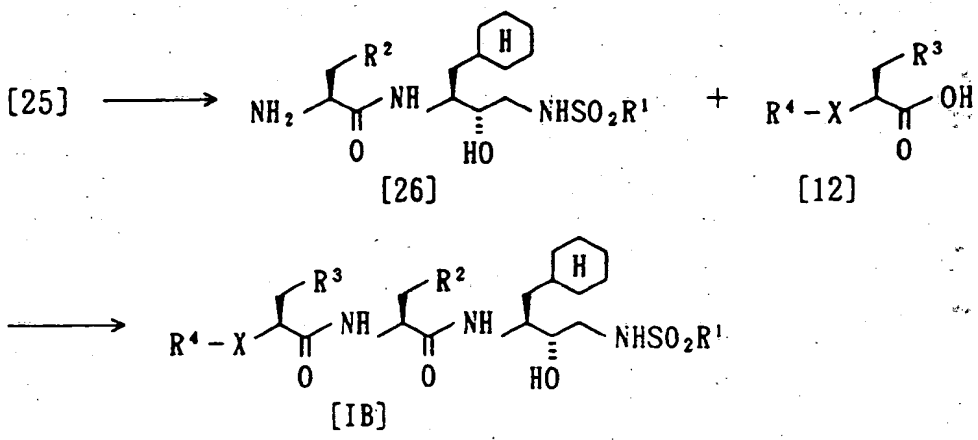
Step 1



Step 2



Step 3



In the above reaction schemes, R^1, R^2, R^3, R^4 and R^7 are as defined above.

Step 1

The optically active aldehyde [1], a required starting compound, can be prepared in the same manner as described in above Process I.

The preparation of cyanhydrin [20] from aldehyde [1] is carried out substantially in accordance with a procedure described in the literature. Thus, the aldehyde [1] is allowed to react with an acidic sodium sulfite to obtain an additive, which is then reacted with KCN in ethyl acetate at room temperature to yield the cyanhydrin [20] stereoselectively (2R/2S = 3/1). The product is then resolved into each stereoisomer by column chromatography on silica gel. The desired (2R)-isomer is a crystalline solid and can be purified by recrystallization while the undesired (2R)-isomer is an oil. Therefore, alternatively, the desired product [20]-2R can be obtained conveniently by adding a seed crystal to the reaction mixture, collecting the precipitate, and recrystallizing from a solvent before subjecting to the chromatography.

The cyanhydrin [20] is then converted into an amino alcohol [21] by reducing the nitrile group. The reduction is carried out effectively by dissolving cyanhydrin [20] into an ethereal solvent, preferably THF, adding about 2 to 2.5 mole of lithium aluminium hydride thereto. The resulting amino alcohol [21] is then, without purification, reacted with sulfonyl chloride [22] to obtain sulfonyl amide of formula [23]. The reaction is conducted by reacting the amino alcohol [21] and sulfonyl chloride [22] in an appropriate solvent such as dichloromethane in th pr -

sence of tertiary amine such as triethylamine at room temperature for overnight.

Step 2

The deprotection of compound [23] can be carried out in a similar manner as describ d in the above Process I. The deprotected compound [24] is, without purification, dissolved into an appropriate solvent such as CH_3CN, or the like, and subjected to a condensation with N-protected-amino acid [8] in the same manner as the coupling reaction described in the above process I to yield a dipeptide analogue [25].

Step 3

The compound [25] is then deprotected in the similar manner as that used for the deprotection of compound [23] in the above Process II, step 2. The product [26] is, without purification, subjected to the condensation reaction with a modified carboxylic acid [12] in exactly the same manner as described in Process I to obtain the final product [IB].

As can be seen from the above reaction schemes, the present invention provides a dipeptide in which one peptide bond is formed through a coupling reaction between, for example, a free carboxyl group of an amino-protected amino acid and an amino group of an amino dihydric alcohol of formula [7] prepared from an oxazolidine derivative of formula [4]. The compound [4], an important intermediate for preparing the compound of formula (I), is obtained by a stereoselective aldol condensation method of the present invention. The other peptide bond is formed by a coupling reaction between a carboxylic group of, for example, sulfonyl propionic acid of formula [12] with a free amino group of a deprotected amino ketone [11] such as histidine as can be seen in the step 4.

As will be hereinafter described in the Experiment, the compounds of the invention have been demonstrated to be an effective renin inhibitor, whereby they suppress the renin-angiotensin system (one of the in vivo causes of hypertension) and lower blood pressure. The compounds of the invention are low in toxicity and useful in the treament of hypertension or cardiac dysfunction through their renin inhibitory activity. The compounds may be administered either orally or parenterally. It is a characteristic benefit of the compounds that they are effective even when orally administered.

When the compounds of the invention are used to treat renin-associated disorders, a therapeutically effective amount of a compound of formula (I) is formulated into a composition of an appropriate form by known procedures using pharmaceutically acceptable carriers, diluents, or excipients. The administration may be conducted orally, intranasally, intravenously, subcutaneously, or the like.

For preparing composition for the administration, an active compound (I) is mixed with one or more standard adducts such as excipient, stabilizer, or inert diluent, and the like. The mixture is then formulated into an appropriate form such as a tablet, coated tablet, hard gelatin capsule, or an aqueous, alcoholic or oily suspension, or an aqueous, alcoholic or oily solution. Examples of inert excipients which can be used include various cyclodextrins, preferably β-cyclodextrin, acacia gum, magnesium carbonate, potassium phosphate, lactose, glucose, magnesium stearyl fumarate, starch, and the like. Either of dry or wet granules can be used. Examples of oily excipients or solvents include vegetable oil such as sunflower oil and fish liver oil.

For subcutaneous or intravenous administration, an active compound or a pharmaceutically acceptable salt thereof is dissolved, dispersed or emulsified into an appropriate solvent with the aid of any substances generally used in such a purpose, for example, solubilizing agent, emulsifying agent, or other adjuncts to obtain solutions, suspensions or emulsions.

Examples of appropriate solvents include water, physiological saline, alcohols such as ethanol, propanediol or glycerol, a sugar solution such as a solution of glucose or mannitol, or a mixture thereof, or Tween 80. Examples of solubilizing agents include above-mentioned cyclodextrins, preferably β-cyclodextrin.

The abbreviations used are as follows:

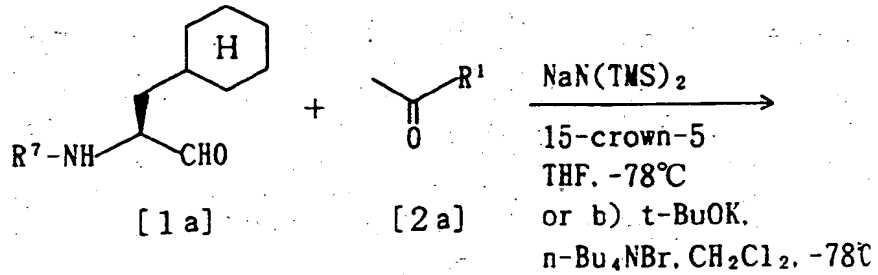
Boc = tertiary-butoxycarbonyl; Red-Al = sodium bis(2-methoxyethoxy)aluminium, L-Selectride = lithium tri-sec-butylborohydride; Boc His(Ts).DCHA = N^{α}-Boc-N^{τ}-tosyl-L-histidine dicyclohexylamine; BOP = benzotriazol-1-yl-oxy-tris-(dimethylamino)phosphoniumhexafluorophosphate;
DCC-HOBt = dicyclocarbodiimide-1-hydroxybenzotriazole;
DCC-HOSu = dicyclohexylcarbodiimide-N-hydroxysuccineimide;
DEPC = diethyl cyanophosphonate; NMM = N-methylmorpholine;
PPTS = pyridinium paratoluenesulphonate;
Tala = (4-thiazolyl)-L-alanine; rt = room temperature;
Ts = tosyl; TMS = trimethylsilane;
DMAP = 4-dimethylaminopyridine;

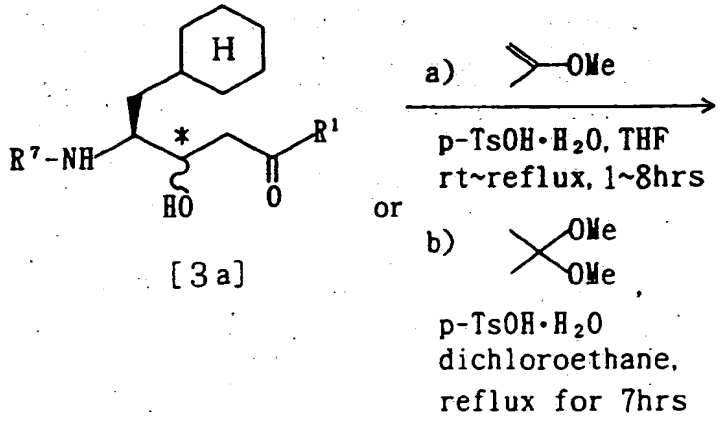
DCHA = Dicyclohexylamine;
DCC = Dicyclohexylcarbodiimide;
EDC = 1-Ethyl-3-(3dimethylaminopropyl)carbodiimide;
DEPA = Diethyl phosphorylazide;
BOP = Benzotriazol-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate

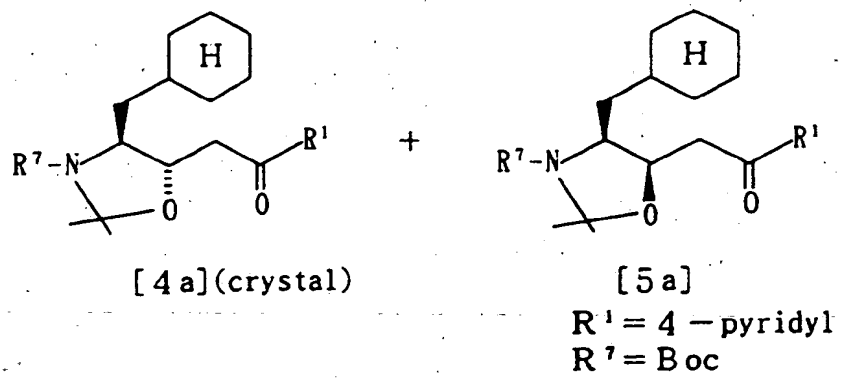
The following Examples further illustrate the compounds of the invention and the processes for preparing the same. The Examples are not intended to be limiting to the scope of the invention in any respect and should not be so construed. Unless otherwise noted, the NMR spectra were measured in $CDCl_3$ at 200 MHz (internal standard = TMS) and IR spectra in $CHCl_3$. All amino acid used are L-isomers.

Preparation 1

3-Boc-4-(S)-cyclohexylmethyl-2,2-dimethyl-5(S)-[2-oxo-2-(4-pyridyl)ethyl]oxazolidine [4a]







1. a) To a 36ml (36mmol, 1.5eq) solution of 1N $NaN(TMS)_2$ in THF is added a solution of 4.34g (36mmol, 1.5 eq) of 4-acetylpyridine [2a] in 20ml of THF at -78°C over 10 minutes under nitrogen atmosphere. After 10 minutes stirring, a solution of 7.898g (36mmol, 1.5 eq) of 15-crown-5 in 10 ml of THF is added thereto and stirred

for 5 minutes. To the mixture is added 6.108g (24 mmol) of N-Boc-L-cyclohexylalaninal [1a] in 50ml of THF over 15 minutes and stirred for 1 hour at -78°C. The reaction mixture is added to a mixture of saturat d aqueous solution of ammonium chloride and ethyl acetate with stirring and extracted three times with thyl acetat . The extract is washed with saturated brin , dried over magnesium sulfate and concentrated to dryness in vacuo. The r sidue, upon purification by column chromatography on silica gel (elu nt; dichloromethane/methanol = 98.5:1.5) gives N-Boc-1 (S)-cyclohexylmethyl-2-hydroxy-4-oxo-4-(4-pyridyl)butylamine [3a] (5.94g; yield = 66.0%) as a colorless powder. The product is a mixture of compound of 2(S)-isomer (desired isomer) and 2(R)-isomer (the ratio of 2(S) : 2(R) = 5.24 : 1).

b) To a stirring solution of 32g (125.3mmol) of N-Boc-L-cyclohexylalaninal [1a], 22.8g (188mmol, 1.5eq) of N-acetylpyridine, and 60.6g (188mmol, 1.5eq) of tetrabutyl ammonium bromide in 700ml of dichrolomethane is added each one fourth portions of t-BuOK (21.1g in total, 188mmol, 1.5eq.) at 10 minutes interval under cooling at -78°C and the stirring is continued for another 1.5 hours at the same temperature. The reaction mixture is added to a mixture of saturated aqueous ammonium chloride and dichloromethane with stirring and extracted three times with dichloromethane. The extract is treated with citric acid to purify the basic substances to obtain a crude product [3a] (37g; yield = 79%; 2(S)/2(R) = 7 : 1).

2. a) To a solution of 5.908g (15.7mmol) of purified alcohol [3a] in 50ml of THF are added 2ml (20.9mmol, 1.3 eq) of 2-methoxypropene and 299mg (1.57mmol, 0.1eq) of p-toluenesulfonic acid monohydrate and the mixture is heated to reflux for 4 hrs. The reaction mixture is concentrated under reduced pressure, and the residue is alkalified with 4% sodium bicarbonate and extracted 3 times with dichloromethane. The extract is washed once with saturated brine, dried over magnesium sulfate, and concentrated to dryness. The residue is decolorized by column chromatography on silica gel using a short column (eluent; dichloromethane/acetonitrile = 5:1) and recrystallized from ethyl acetate to obtain 4.66g (yield = 68.6%) of the title compound [4a] as a colorless solid.

b) A mixture of 72g (195.6mmol) of the crude alcohol [3a], 150ml (122.0mmol, 6.2eq) of 2,2-dimethoxypropane and 2.73g (14.4mmol, 0.073eq) of p-toluenesulfonic acid monohydrate in 150ml of dichloroethane is heated to reflux for 16 hours. After cooling, the mixture is made basic with 4% aqueous sodium bicarbonate and extracted 3 times with dichloromethane. The extract is washed once with saturated brine, dried over magnesium sulfate, and concentrated to dryness in vacuo. The crude product, upon recrystallization from isopropyl ether, gives 23.5g (29.5%) of the compound [4a] as a white crystal. The mother liquor, when treated by column chromatography on 300g of silica gel (eluent; dichloromethane/ethyl acetate = 7:1) and recrystallized in the same manner as above, gives 2.5g (3.1%) of compound [4a].

m.p. = 115 - 116°C

$[\alpha]_D$ = -18.5° (C=1.0 $CHCl_3$; 23.5°C)

IRνmax($CHCl_3$):1692, 1596, 1557, 1477, 1450, 1172, 1086 cm^{-1}

NMRδ ($CDCl_3$):1.48(9H,s), 1.52(3H,s), 1.60(3H,s), 0.78-1.90(13H,m), 3.14(1H,dd,J=16.8,6.8Hz), 3.41(1H,dd,J=16.7,6.1Hz), 3.84(1H,m), 4.52(1H,t like m), 7.73(2H,m), 8.83(2H,m)

Elemental analysis (as $C_{24}H_{36}N_2O_4$)

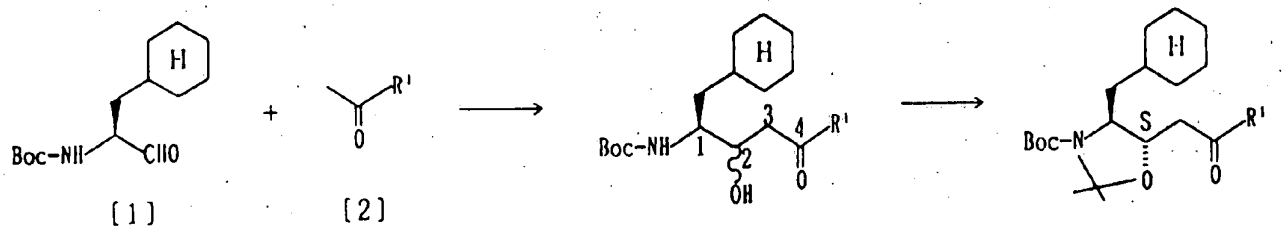
Calcd.(%): C:69.20; H:8.71; N:6.73

Found (%): C:69.20; H:8.75; N:6.76

Preparation 2 - 20

Compounds [4], the desired stereoisomers, were prepared according to the method described in above Preparation 1 by preparing compound [3a] and separating the desired isomer [3]-(S) therefrom. The results are shown in the following Table 1. Among the compounds listed in the Table 1, compound Nos. 13 and 14 are separated chromatographically because the corresponding compounds of formula [4] do not crystallize under the conditions used.

Table 1



[1] [2] [3] [4]

Compd. of Prep. No.	R'	[3]		[4]							
		Yield%	C-2 S/R	Yield%	mp℃	$[\alpha]_D^{\cdot}$ C=1.0, $CHCl_3$ (℃)	Elemental analysis	Calcd.	Found	I R ν cm^{-1} max
2	phenyl	71	3.1	70	111~113	-17.4 (23.5)	$C_{26}H_{37}NO_4$	C:72.25 H: 8.98 N: 3.37	C:72.25 H: 8.99 N: 3.36	1686, 1650, 1582, 1478, 1450, 1172, 1088
3	o-fluorophenyl	68	4.8	75	95~97	-18.5 (24.0)	$C_{26}H_{36}NO_4F$	C:69.25 H: 8.37 N: 3.23 F: 4.38	C:69.12 H: 8.10 N: 3.23 F: 4.45	1686, 1610, 1577, 1480, 1453, 1173, 1100, 1086, 990, 848
4	m-methoxyphenyl	75	2.7	80	117~119	- 6.2 (23.5)	$C_{27}H_{39}NO_5$	C:70.08 H: 8.82 N: 3.14	C:70.05 H: 8.74 N: 3.15	1689, 1600, 1585, 1488, 1465, 1456, 1430, 1394, 1369, 1290, 1255, 1172, 1139, 1088, 1050
5	p-methylphenyl	78	2.4	69	132~134	-23.5 (24.0)	$C_{27}H_{39}NO_4$	C:72.69 H: 9.15 N: 3.26	C:72.66 H: 9.08 N: 3.20	1687, 1610, 1573, 1480, 1450, 1174, 1088,
6	2,4-difluorophenyl	91	4.8	69	136~137	-19.1 (23.5)	$C_{26}H_{35}NO_4F_2$	C:66.49 H: 7.81 N: 3.10 F: 8.42	C:66.31 H: 7.82 N: 3.04 F: 8.38	1687, 1612(1595), 1498, 1477, 1450, 1430, 1172, 1140, 1098, 971, 855

Table 1 (continued)

Compd. of Prep. No.	R¹	[3] Yield%	[3] C-2 S/R	[4] Yield%	[4] mp℃	[4] [α]D (C=1.0, CHCl3) (℃)	[4] Elemental analysis	Calcd.	Found	IR ν max cm⁻¹
7	1-naphthyl	90	1.7	60	127~128	-11.7 (24.0)	$C_{29}H_{33}NO_4$	C:74.81 H:8.44 N:3.01	C:74.84 H:8.43 N:3.06	1687, 1595, 1508, 1477, 1449, 1393, 1379, 1368, 1250, 1172, 1138, 1098, 1085
8	3-thienyl	80	2.7	62	113~114	-13.5 (25)	$C_{23}H_{33}NO_4S$	C:65.52 H:8.37 N:3.32 S:7.61	C:65.75 H:8.28 N:3.31 S:7.57	1685, 1510, 1477, 1450, 1172, 1088
9	2-thiazolyl	75	16	72	128~129	-10.7 (23.5)	$C_{22}H_{34}N_2O_4S$	C:62.53 H:8.11 N:6.63 S:7.59	C:62.28 H:7.79 N:6.53 S:7.36	1690, 1480, 1448, 1170, 1075, 945

Table 1 (continued)

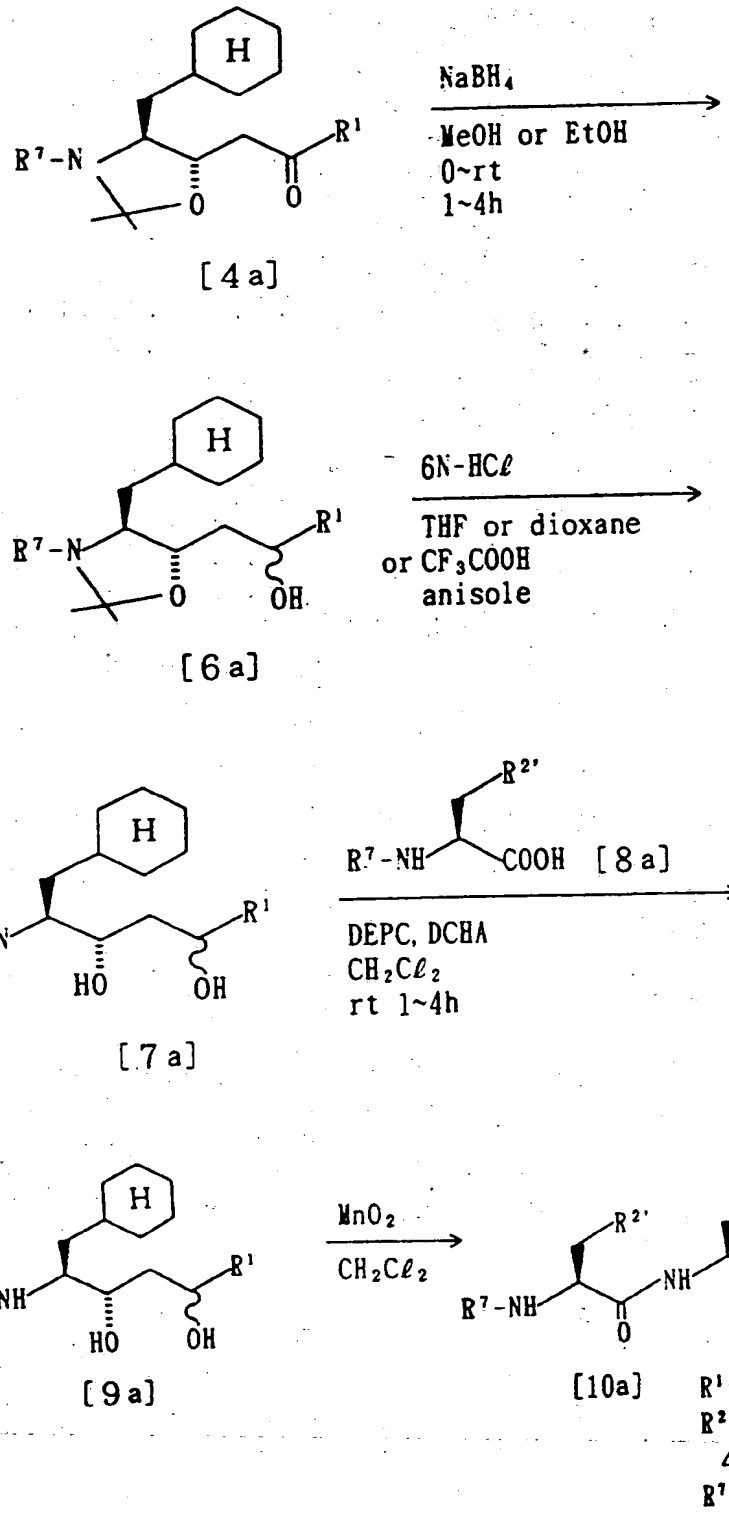
Compd. of Prep. No.	R¹	[3] Yield%	[3] C-2 S/R	[3](S) or [4] Yield%	mp℃	[α]D²⁴ C=1.0, CHCℓ₃	Elemental analysis	Calcd.	Found	IR νmax cm⁻¹ or NMR(δ)
10	m-fluorophenyl	82	3.9	71	103~105	-15.7°	$C_{25}H_{30}N_1O_4F$	C:69.25 H: 8.37 N: 3.23 F: 4.38	C:69.36 H: 8.41 N: 3.25 F: 4.22	1690, 1610, 1590, 1485, 1475, 1443, 1392, 1170, 1086
11	p-fluorophenyl	83	2.8	61	137~138	-15.7°	$C_{25}H_{30}N_1O_4F$	C:69.25 H: 8.37 N: 3.23 F: 4.38	C:69.14 H: 8.35 N: 3.14 F: 4.41	1685, 1600, 1505, 1475, 1450, 1392, 1170, 1155, 1085
12	2,6-difluorophenyl	88	13.0	83	51~54	-18.8°	$C_{25}H_{29}N_1O_4F_2$	C:66.50 H: 7.81 N: 3.10 F: 8.41	C:66.40 H: 7.79 N: 3.34 F: 8.69	1691, 1624, 1588, 1467, 1450, 1394, 1369, 1279, 1174, 1139, 1089, 1030, 982, 860
13	o-methoxyphenyl	79	2.8	[3](S) 53						0.75~1.93(13H, m), 1.45(9H, s), 3.10(1H, dd, J=9.9, 18.3Hz), 3.70(1H, m), 4.16(1H, m), 4.82(1H, d, J=10Hz), 7.00(2H, m), 7.50(1H, td, J=2.5, 7Hz), 7.75(1H, dd, J=2.5, 7Hz)
14	o-chlorophenyl	86	3.0	[3](S) 57		-36.8°				0.74~1.90(13H, m), 1.44(9H, m), 3.18(2H, m), 3.71(1H, m), 4.20(1H, m), 4.75(1H, d, J=10Hz), 7.22~7.59(4H, m)
15	m-cyanophenyl	70	2.8	68	114~117	-14.7°	$C_{26}H_{30}N_2O_4$	C:70.88 H: 8.24 N: 6.36	C:70.87 H: 8.27 N: 6.16	2236, 1693, 1602, 1479, 1450, 1394, 1369, 1172, 1088
16	p-methyl-sulfonyl-aminophenyl	67	1.5	51	131~132	-3.3°	$C_{26}H_{40}N_2O_6S$	C:61.39 H: 7.93 N: 5.51 S: 6.30	C:61.00 H: 7.85 N: 5.48 S: 6.22	1691, 1656, 1607, 1578, 1496, 1453, 1394, 1369, 1342, 1279, 1156, 1089, 967, 918

Table 1 (continued)

Compd. of Prep. No.	R¹	[3] Yield%	[3] C-2 S/R	[4] Yield%	[4] mp℃	[4] [α]D* C=1.0, CHCℓ3 (℃)	[4] Elemental analysis	Calcd.	Found	IR (ν max cm⁻¹)
17	p-trifluoromethylphenyl	75	4.9	80	128~130	-1.6 (24)	$C_{26}H_{34}F_3NO_4$	C:64.58 H: 7.50 N: 2.90 F:11.79	C:64.83 H: 7.54 N: 2.89 F:12.02	1690, 1582, 1510, 1450, 1325, 1172, 1137, 1066
18	m-morpholinocarbonylphenyl	70	2.7	80	154~157	-3.6 (23)	$C_{30}H_{44}N_2O_6$	C:68.16 H: 8.39 N: 5.30	C:68.04 H: 8.44 N: 5.36	1690, 1632, 1484, 1451, 1438, 1394, 1369, 1303, 1277, 1172, 1141, 1116, 1087, 1025
19	m-(N-morpholino)-ethoxyphenyl	71	3.0	39	117~119	-13.5 (23.5)	$C_{31}H_{48}N_2O_6 \cdot 1/4\ H_2O$	C:67.33 H: 8.90 N: 5.10	C:67.55 H: 8.72 N: 5.06	1686, 1650, 1582
20	m-(N-2-formyl)-methylaminophenyl	85	2.8	53	117~118	-16.5 (24.0)	$C_{27}H_{40}N_2O_5$	C:68.62 H: 8.53 N: 5.93	C:68.68 H: 8.43 N: 5.93	1680, 1602, 1585, 1486, 1476, 1447, 1393 1378, 1367

Preparation 21

Boc-His(Ts)-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(4-pyridyl)butylamide [10a]



To a 3-Boc-4-(S)-cyclohexylmethyl-2,2-dimethyl-5(S)-[2-oxo-2-(4-pyridyl)ethyl]oxazolidine[4a](4.66g, 11.18mmol) is dissolved in ethanol (20ml) is added sodium borohydride (508mg, 13.42mmol) with stirring and

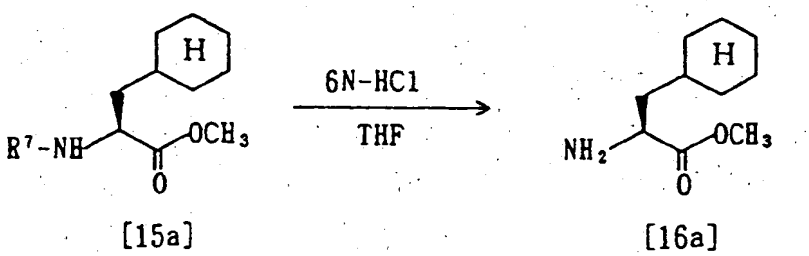
ice-cooling and the mixture is allowed to react at room temperature for one hour. The solvent is removed in vacuo. To the residue are added ice water and saturated aqueous ammonium chloride, and the mixture is extracted with dichloromethane three times. The organic layer is washed with saturated aqueous sodium chloride, dried over $MgSO_4$, and vaporated to dryness in vacuo to obtain 3-Boc-4(S)-cyclohexylmethyl-2,2-dimethyl-5(S)-[2-hydroxy-2-(4-pyridyl)ethyl]oxazolidine [6a] (4.88g, quantitative amount) in colorless powder. The product is then, without further purification, dissolved in THF (2ml), and 6N HCl (16ml) is added thereto, and the mixture is stirred at room temperature for one hour. The reaction mixture is neutralized with 6N NaOH, alkalified with sodium bicarbonate, and then extracted five times with dichloromethane containing 10% methanol. The extract is dried over $MgSO_4$ and evaporated to dryness in vacuo to obtain 1(S)-cyclohexylmethyl-2(S), 4-dihydroxy-4-(4-pyridyl)butylamine [7a] (3.3g, quantitative amount, diastereomer ratio 1:1) in colorless powder. The product (3.30g) is then, without further purification, dissolved in dichloromethane (100ml). To the solution are added Boc-His(Ts).DCHA [8a] (8.3g, 14.05mmol, 1.3eq) and diethyl cyanophosphonate (2.29g, 14.05mmol, 1.3eq), and the mixture is stirred for 6 hours at room temperature. The reaction mixture is evaporated to dryness in vacuo, and the residue is purified with silica gel chromatography (CH_2Cl_2:MeOH = 95:5) to obtain Boc-His(Ts)-1(S)-cyclohexylmethyl-2(S), 4-dihydroxy-4-(4-pyridyl)butylamide [9a] (6.00g, 80%) as a mixture of two diastereomers. The product [9a] may be used in the following reaction without separation of the two isomers.

To the solution of product [9a] (1.0g, 1.45mmol) in dichloromethane (3ml) is added MnO_2 (5g) at room temperature, and the mixture is stirred for six hours. The resultant black suspension is filtered on a Celite layer overlaid with active carbon, and insoluble material on the layer is thoroughly washed with CH_2Cl_2-MeOH (10:1). The filtrate is evaporated to dryness in vacuo and purified with silica gel chromatography (CH_2Cl_2:MeOH = 95:5) to obtain the title compound [10a] (683mg, 69%) in colorless powder.

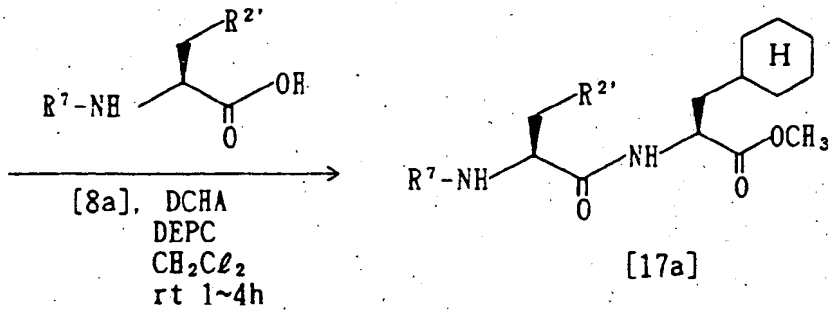
NMR $\delta(CDCl_3)$: 1.34(9H,s), 0.70-2.20(13H,m), 2.45(3H,s), 2.99(2H,m), 3.03(1H,dd,J=17.8,2.3Hz), 3.34(1H,dd,J=17.8,9.6Hz), 4.04(1H,ddd,J=8.7,8.7,8.7Hz), 4.23(1H,m), 4.30(1H,ddd,J=5.8,5.8,5.8Hz), 6.16(1H,m), 6.47(1H,d,J=10Hz), 7.11(1H,s), 7.36(2H,d,J=8Hz), 7.80(2H,m), 7.81(2H,d,J=8.6Hz), 7.92(1H,s), 8.82(2H,d,J=5Hz)

IR $\nu(CHCl_3)$max cm^{-1}: 3680, 3420, 3300(br), 1700, 1670, 1625, 1598, 1555, 1492, 1450, 1410, 1385, 1370, 1180, 1080, 1010

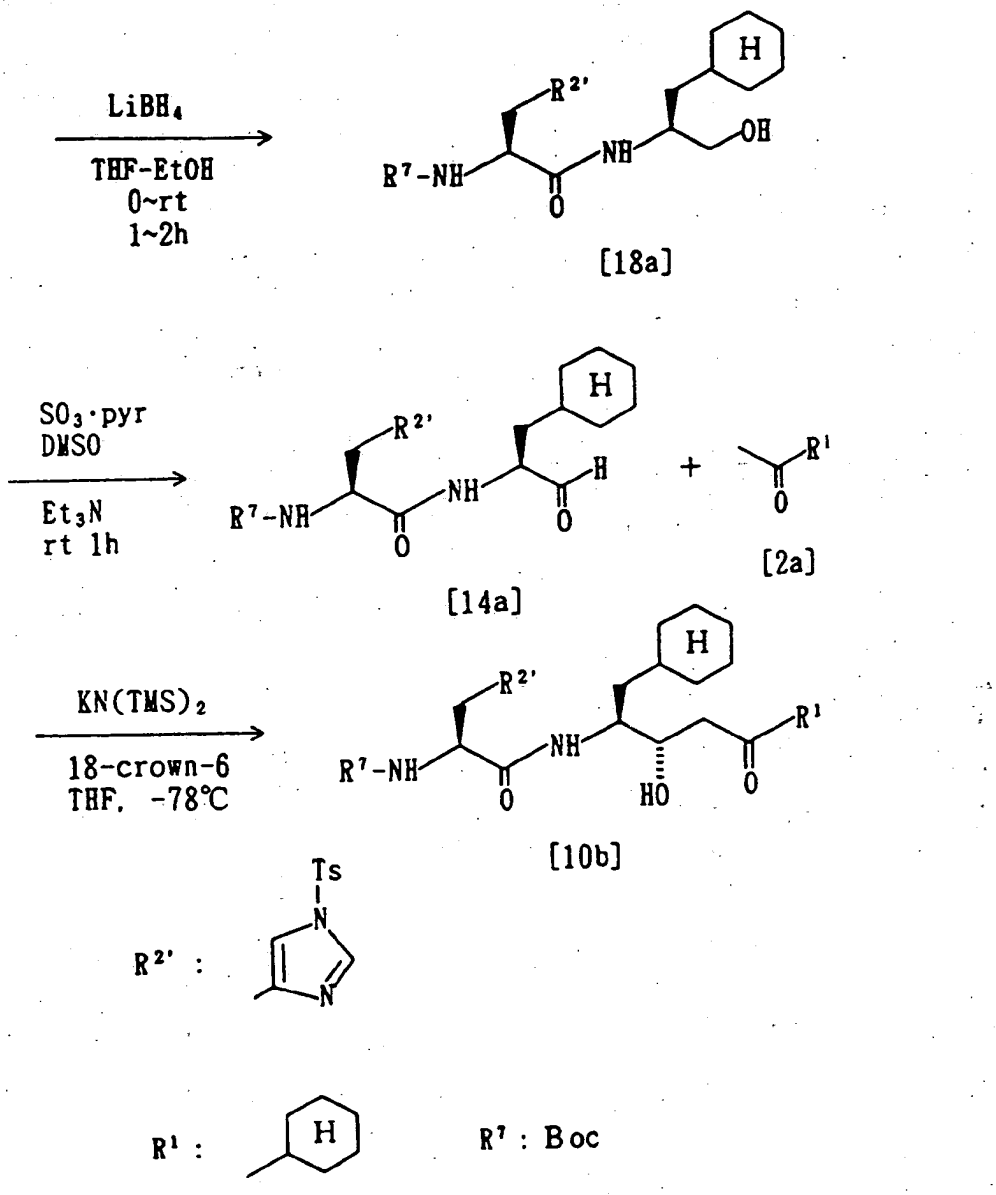
Preparation 22



[15a] [16a]



[17a]



A solution of N-Boc-3-cyclohexyl-alanine methyl ester [15a] (4.00g, 13.93mmol) in THF (10ml) is stirred in the presence of 6N HCl (40ml) at room temperature for four hours. The reaction mixture is made alkaline with powdery sodium bicarbonate and extracted with dichloromethane containing 5% methanol (100 ml x 4).

The extract is dried over $MgSO_4$ and evaporated to dryness in vacuo to quantitatively obtain 3-cyclohexylalanine methyl ester [16a] as an oil. The product is then, without further purification, dissolved in dichloromethane (50ml). To the solution are added Boc-His(Ts).DCHA [8a] (10.7g, 18.11mmol, 1.3eq) and diethyl cyanophosphonate (2.95g, 18.1mmol, 1.3eq), and the mixture is stirred for 1.5 hours at room temperature. The reaction mixture is subjected to silica gel chromatography (SiO_2:300g, CH_2Cl_2:MeOH = 99:1) to give a purified Boc-His(Ts)-3-cyclohexylalanine methyl ester [17a] (7.43g, 93%) as an oil. To a solution of the dipeptide ester [17a] (3.0g, 5.2mmol) in THF (6ml) and ethanol (6ml) is added a 2N solution of lithium borohydride in THF (3ml, 6mmol) with stirring and ice-cooling. After 20 minutes stirring, the mixture is allowed to react at room t mperature for an additional one hour. The solvent is removed in vacuo and to the residue is added ic water and saturated aqueous ammonium chloride followed by extraction with dichloromethane (20ml x 3). The organic layer is washed with saturated aqueous sodium chloride, dried over $MgSO_4$, evaporated to dryness in vacuo and the residue is purified by silica gel chromatography (SiO_2: 200g, CH_2Cl_2:MeOH = 98:2) to obtain Boc-His(Ts)-3-cyclohexyl-alaninol [18a] (2.06g, 72%) as an oil.

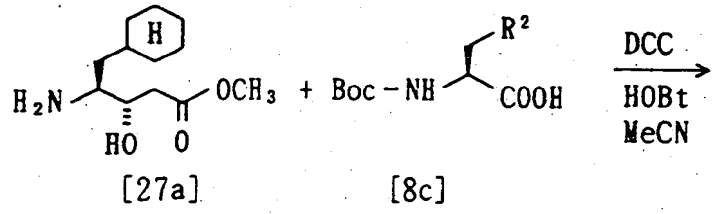
To a mixture of the dipeptide alcohol [18a] (2.0g, 3.65mmol), triethylamine (1.30g, 12.85mmol, 3.5eq) and

DMSO (6ml) is added at room temperature SO_3·pyridin (2.03g, 12.75mmol, 3.5eq) in DMSO (6ml) and the mixture is stirred for 35 minutes. The reaction mixture is poured on ice, and the resultant aqueous mixture is extract d with thyl acetate (20ml x 3). The organic layer is subsequently washed with 10% aqueous citric acid, saturated aqueous sodium chloride (x 2), 7% aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried ver $MgSO_4$, and concentrated to dryn ss in vacuo. The resultant residue is purified with silica gel chromatography (SiO_2:100g, CH_2Cl_2:MeOH = 95:5) to obtain Boc-His(Ts)-3-cyclohexylalaninal [14a] (1.67g, 84%) in amorphous powder.

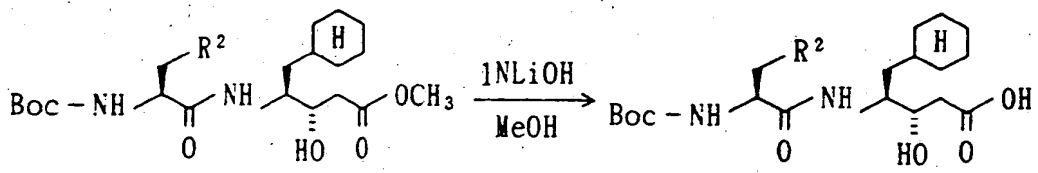
To a 0.5N potassium bis-trimethylsilylamide solution in toluene (9.2ml, 4.60mmol, 2.5eq) is added dropwise at -78°C cyclohexyl methyl ketone (0.58g, 4.60mmol, 2.5eq) in THF (9ml) with stirring under a nitrogen atmosphere over 10 minutes. After 20 minutes stirring at the same temperature, 18-crown-6 (1.216g, 4.60mmol, 2.5eq) in THF (10ml) is dropwise added to the mixture over two minutes. Further, the dipeptidealdehyde [14a] (1.0g, 1.83mmol) in THF (10ml) is dropwise added over 15 minutes at -78°C, and the mixture is stirred for one hour at the same temperature. The reaction is quenched by adding a solution of acetic acid (0.60g, 10mmol, 5.5eq) in THF (10ml) and after the addition of saturated aqueous ammonium chloride (30ml) the mixture is extracted with ethyl acetate (50ml x 3). The organic layer is washed with saturated aqueous sodium chloride, dried over $MgSO_4$, concentrated to dryness in vacuo, and purified with silica gel chromatography (Lobar column, CH_2Cl_2:MeOH = 95:5) to obtain Boc-His(Ts)-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-cyclohexyl-butylamide [10b] (0.18g, 15%) in amorphous powder.

NMR δ: 1.30-1.90(23H,m), 1.40(9H,s), 2.32(1H,m), 2.44(3H,s), 2.59(2H,m), 2.93(1H,dd,J=5.8,9.6Hz), 3.04(1H,dd,J=5.8,9.6Hz), 3.89(1H,ddd,J=8.4,8.4,8.4Hz), 3.98(1H,m), 4.30(1H,ddd,J=6.0,6.0,6.0Hz), 6.12(1H,d,J=6.0Hz), 6.47(1H,d,J=9.8Hz), 7.10(1H,d,J=0.8Hz), 7.36(2H,d,J=8.0Hz), 7.81(2H,d,J=8.4Hz), 7.93(1H,d,J=1.2Hz)

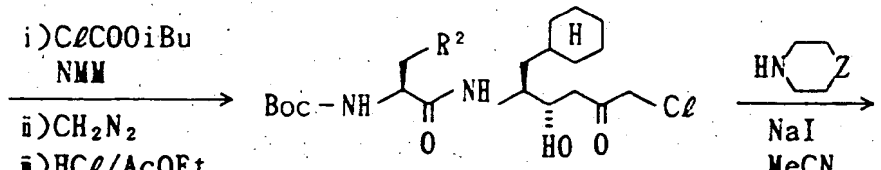
Preparation 23



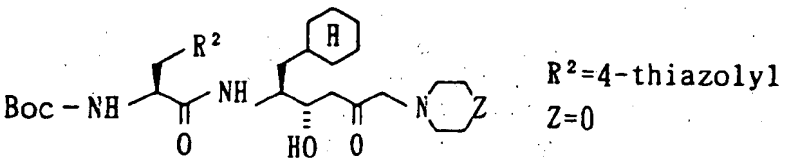
[27a] [8c]



[28a] [29a]



[19a]



R²=4-thiazolyl
Z=O

[10c]

To a solution of cyclostatine methyl ester [27a] (700mg, 3.05mmol), Boc-(4-thiazolyl)-L-alanine [8c] (869mg, 3.19mmol, 1.05eq), and HOBt (431mg, 3.19mmol, 1.05eq) in CH_3CN (10ml) is added DCC (660mg, 3.20mmol, 1.05eq) with stirring and ice-cooling under nitrogen atmosph re and the mixture is stirred for 1.5 hours at the same temperature and then allowed to react at room temperature for 14 hours. Ethyl acetate is added to th mixture, and precipitated crystals were filter d off. Th filtrate is concentrated to dryness in vacuo and the residue is subjected to silica gel chromatography (SiO_2:100g, NH_4OH:MeOH:CH_2Cl_2 = 1:10:990) to give the aimed product, Boc-(4-thiazolyl)alanyl-cyclostatine methyl ester [28a] (830mg, 59%) as an oil.

To the solution of the above product [28a] (830mg, 1.72mmol) in MeOH (2ml) is added 1N LiOH (1.9ml, 1.9mmol, 1.1eq) with stirring and ice-cooling. The mixture is stirred for 10 minutes and allowed to react at room temperature for two hours. After neutral substances are removed by washing with dichloromethane, the mixture is acidified with citric acid and is extracted with ethyl acetate. The organic layer is dried over $MgSO_4$, and concentrated to dryness in vacuo to obtain the aimed carboxylic acid [29c] (700mg, 87%).

To a mixture of the above carboxylic acid [29a] (700mg, 1.67mmol) and N-methylmorpholine (0.17ml, 1.67mmol) in THF (10ml) is added isobutyl chlorocarbonate (0.2ml, 1.67mmol) with stirring at a temperature of -15°C - -10°C under nitrogen atmosphere, and the resultant mixture is stirred for 50 minutes at the same temperature. After precipitated crystals are removed by filtration, to the filtrate is added a solution of diazomethane (2.2eq) in ethyl ether previously prepared at -10°C and allowed to reaet at room temperature for 3 hours. The reaction mixture is concentrated in vacuo to remove diazomethane and ethyl acetate (10ml) is added to the residue. After addition of 2N HCl (3ml) at -40°C - -30°C, the mixture is allowed to react for one hour. The reaction mixture is alkalified by addition of saturated aqueous sodium bicarbonate and the ethyl acetate layer is separated. The layer is dried over $MgSO_4$ and concentrated to dryness in vacuo to obtain 800mg of crude chloromethyl ketone [19a]. Since the product tends to get colored and decomposed, it is immediately used in the next step without purification.

To a solution of the above product [19a] (400mg) in MeCN (5ml) are added morpholine (150mg) and a catalytic amount of NaI, and the mixture is stirred at room temperature for two hours. The reaction mixture is purified by chromatography to give the aimed compound, Boc-(4-thiazolyl)alanyl-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(N-morpholino)methyl-butylamide [10c] (Z=0) (120mg, 29% starting from [29a]).
NMRδ: 0.6-2.00(13H,m), 1.43(9H,s), 2.55(4H,m), 3.22(2H,dd,J=4.6,14.8Hz), 3.26(2H,s), 3.43(1H,dd, J= 5.4,14.8Hz), 3.76(4H,m), 3.89(1H,m), 3.94(1H,m), 4.44(1H,ddd,J=6.2HzX3), 6.38(1H,d,J=9.8Hz), 6.48 (1H, d, J=7.5Hz),7.13(1H,d,J=1.8Hz), 8.79(1H,d,J=2Hz)

Preparation 24

In the same manner as in Preparation 23, Boc-(4-thiazolyl)alanyl-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(N-piperidino)methyl-butylamide [10d] (Z=CH_2) is obtained with an overall yield of 29%.
NMRδ: 0.6-1.83(19H,m), 1.44(9H,s), 2.46(4H,m), 3.15(2H,s), 3.20(1H,dd,J=5.6,14.8Hz), 3.44(1H, dd, J= 5,14.8Hz), 3.89(2H,m), 4.47(1H,m), 6.41(1H,bs), 6.43(1H,d,J=9.8Hz), 7.12(1H,d,J=1.8Hz), 8.78 (1H, d, J= 1.8Hz)

Preparation 25-50

Starting from the compounds [4] which have been prepared in Preparations 2-20, the ketone compounds [10] are obtained in the same manner as in Preparation 21. The thus obtained products are listed in Table 2.

Preparation 51-57

The aldol reaction between dipeptides [14] and methyl ketones [2] gives ketone compounds [10] in the same manner as in Preparation 22. The thus obtained products are listed in Table 3.

Table 2

Compd. of Prep. No.	R'	R²'	[9] Yield% (from [7])	[10] Yield%	[10] IR ν max cm⁻¹ or NMR (δ)
25	phenyl		82	65	3680. 3420. 3300. 3140. 1705. 1675. 1625. 1600. 1580. 1495. 1450. 1370. 1162. 1125. 1032. 1010
26	o-fluorophenyl		92	51	3680. 3420. 3280. 3140. 1675(1700sh), 1625. 1610. 1492. 1450. 1390. 1370. 1160. 1132. 1030. 1010
27	m-methoxyphenyl		100	43	0. 7~1. 85(13H, m), 1. 34(9H, s), 2. 44(3H, s), 2. 95~3. 55(2H, m), 2. 99(2H, m), 3. 86(3H, s), 4. 02(1H, ddd, J=9. 9, 9Hz), 4. 20(1H, d, J=10Hz), 4. 32(1H, ddd, 6. 6Hz), 6. 09(1H, m), 6. 56(1H, d, J=10Hz), 7. 11(1H, d, J=1. 3Hz), 7. 12(1H, m), 7. 35(2H, d, J=8Hz), 7. 48(1H, m), 7. 55(1H, m), 7. 37(1H, m), 7. 80(2H, d, J=8. 4Hz), 7. 93(1H, d, J=1. 4Hz)

Table 2 (continued)

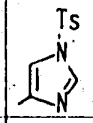
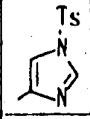
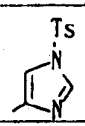
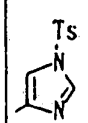
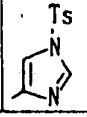
Compd. of Prep. No.	R¹	R²'	[9] Yield% (from[7])	Yield%	[10] IR νmax cm⁻¹ or NMR(δ)
28	p-methylphenyl		78	57	3420. 3300. 3240. 1705. 1670. 1625. 1608. 1495. 1450. 1370. 1122. 1033. 1010
29	2,4-difluorophenyl		72	50	3680. 3420. 3300(br). 1705. 1672. 1611. 1599. 1496. 1450. 1430. 1384. 1370. 1172. 1095. 1080. 970. 855
30	1-naphthyl		71	50	3692. 3420. 1709. 1673. 1599. 1575. 1495. 1450. 1386. 1370. 1175. 1094. 1080. 1033. 979. 908
31	3-thienyl		48	63	0.7~1.85(13H, m), 1.34(9H, s), 2.44(3H, s), 2.99(2H, m), 2.86~3.27(2H, m), 4.00(1H, ddd, J=9.9, 9Hz), 4.19(1H, d, J=10Hz), 4.32(1H, ddd, J=6.6, 6Hz), 6.15(1H, d, J=5.0Hz), 6.54 (1H, d, J=9Hz), 7.11(1H, d, J=1.2Hz), 7.36(2H, d, J=8.2Hz), 7.3(1H, dd, J=2.8, 5.2Hz), 7.53(1H, dd, J=1.2, 5.2Hz), 7.80(2H, d, J=8.4Hz), 7.91(1H, d, J=1.2Hz), 8.18(1H, m)
32	2-thiazolyl		79	5	3420. 3300. 3140. 1703. 1670. 1625. 1603. 1550(br). 1496. 1450. 1370. 1165. 1123. 1032. 1010

Table 2 (continued)

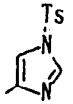
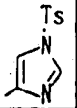
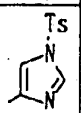
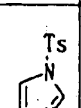
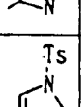
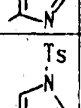
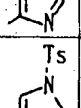
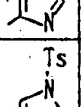
Compd. of Prep. No.	R¹	R²'	[9] Yield% (from[7])	Yield%	[10] IR ν max cm⁻¹, NMR(δ), [α]ᴅ°, m.p.
33	m-fluorophenyl		76	45	3420. 3280. 3140. 1675. 1625. 1590. 1495. 1160. 1122. 1030. 1010
34	p-fluorophenyl		78	61	3420. 3320. 3140. 1670(sh1705). 1625. 1600. 1495. 1155. 1030. 1010
35	2, 6-difluorophenyl		88	30	3424. 1707. 1676. 1625. 1598. 1495. 1468. 1386. 1370. 1174. 1094. 1080. 1028 [α]ᴅ -6. 0°(C=1. 0. CHCℓ₃. 24℃)
36	o-methoxyphenyl		31	55	0. 75~1. 83(13H. m). 1. 36(9H. s). 2. 44(3H. s). 3. 00(2H. m). 3. 13(2H. m). 3. 90(3H. s). 3. 96(1H. ddd. J=10. 10. 10Hz). 4. 15(1H. m). 4. 34(1H. ddd. J=7. 7. 7Hz). 6. 04(1H. d. J=7Hz). 6. 58(1H. d. J=10Hz). 6. 99(2H. m). 7. 10(1H. d. J=1. 2Hz). 7. 35(2H. d. J=8. 6Hz). 7. 47(1H. m). 7. 70(1H. dd. J=2. 7. 8Hz). 7. 80(2H. d. J=8. 4Hz). 7. 91(1H. d. J=1. 4Hz)
37	o-chlorophenyl		85	27	0. 74~1. 82(13H. m). 1. 39(9H. s). 2. 44(3H. s). 2. 98(2H. m). 3. 08(2H. m). 3. 99(1H. m). 4. 18 (1H. m). 4. 30(1H. ddd. J=7Hz). 6. 05(1H. d. J=7Hz). 6. 52(1H. d. J=10Hz). 7. 10(1H. d. J=1. 3Hz). 7. 27~7. 45(6H. m). 7. 60(1H. m). 7. 80(2H. d. J=8. 4Hz). 7. 90(1H. d. J=1. 4Hz)
38	m-cyanophenyl		67	51	3420. 2236. 1709. 1678. 1599. 1495. 1451. 1432. 1387. 1371. 1174. 1093. 1081. 909
39	o-methyl-sulfonyl-aminophenyl		76	58	3424. 1709. 1672. 1599. 1578. 1496. 1452. 1385. 1371. 1341. 1174. 1155. 1094. 1081. 1034. 968. 917
40	p-trifluoro-methyl-phenyl		74	37	3420. 1705. 1675. 1625. 1575. 1325. 1170. 1135. 1080. 1065 m.p. =133~135℃

Table 2 (continued)

Compd. of Prep. No.	R¹	R²	[9] Yield% (from[7])	[10] Yield%	[10] IR νmaxcm⁻¹ またはNMR(δ)
41	m-morpholino-carbonylphenyl		85	68	3420. 1709. 1674. 1632. 1600. 1495. 1386. 1370. 1279. 1174. 1116. 1093. 1080. 1026
42	phenyl		90	57	0. 70~1. 90(13H, m), 1. 34(9H, s), 2. 90~3. 60(4H, m), 3. 99(1H, m), 4. 16(1H, m), 4. 49(1H, ddd, J=6. 2, 6. 2, 6. 2Hz), 6. 46(1H, d, J=9. 2Hz), 7. 12(1H, d, J=1. 8Hz), 7. 40~7. 63(3H, m), 7. 96(2H, d, J=8. 4Hz), 8. 76(1H, d, J=2Hz)
43	4-pyridyl		90	64	0. 70~2. 05(13H, m), 1. 34(9H, s), 2. 95~3. 50(4H, m), 4. 01(1H, m), 4. 19(1H, m), 4. 46(1H, ddd, J=5. 8Hz), 6. 4(1H, d, J=8Hz), 6. 55(1H, d, J=5Hz), 7. 13(1H, d, J=1. 8Hz), 7. 78(2H, d, J=6. 2Hz), 8. 77(1H, d, J=1. 8Hz), 8. 80(1H, d, J=9. 4Hz)
44	3-thienyl		86	80	0. 65~2. 05(13H, m), 1. 36(9H, s), 2. 93(1H, d, J=17. 1Hz), 3. 15(1H, dd, J=17. 6, 9. 4Hz), 3. 22(1H, dd, J=14. 8, 5. 4Hz), 3. 44(1H, dd, J=14. 6, 5. 3Hz), 3. 97(1H, m), 4. 15(1H, m), 4. 48(1H, ddd, J=6. 4, 6. 4, 6. 4Hz), 6. 44(1H, d, J=9. 9Hz), 6. 50(1H, d, J=7. 5Hz), 7. 12 (1H, d, J=1. 9Hz), 7. 30(1H, dd, J=5. 1, 2. 9Hz), 7. 53(1H, dd, J=5. 1, 1. 3Hz), 8. 20(1H, d, J=1. 9Hz), 8. 77(1H, d, J=2. 1Hz)
45	m-2-(N-morpholino)-ethoxyphenyl		96	51	0. 70~1. 90(13H, m), 1. 35(9H, s), 2. 60(4H, m), 2. 83(2H, t, J=5. 4Hz), 3. 17(2H, m), 3. 22(1H, dd, J=4. 6, 14. 4Hz), 3. 44(1H, dd, J=5. 2, 14. 6Hz), 3. 75(4H, m), 3. 98(1H, ddd, J=6. 2, 6. 2, 6. 2Hz), 4. 49(3H, m), 4. 49(1H, ddd, J=6. 2, 6. 2, 6. 2Hz), 6. 45(2H, d, J=9. 8Hz), 7. 11(1H, d, J=2. 0), 7. 15(1H, dd, J=1. 2, 2. 8Hz), 7. 37(1H, t, J=7. 8Hz), 7. 48(1H, m), 7. 56(1H, d, J=7. 8Hz), 8. 77(1H, d, J=2. 0Hz)
46	m-(N-formyl)-methylamino		97	77	0. 70~1. 86(13H, m), 1. 33(9H, s), 3. 00(1H, dd, J=0. 5, 14. 8Hz), 3. 23(1H, dd, J=5. 2, 14. 8Hz), 3. 36(3H, s), 3. 40(3H, m), 4. 01(1H, m), 4. 20(1H, d, J=9. 8Hz), 4. 47(1H, ddd, J=5Hz), 6. 44(1H, d, J=9. 8Hz), 6. 58(1H, d, J=6. 4Hz), 7. 14(1H, d, J=1. 8Hz), 7. 39(1H, ddofd, J=1. 2, 2. 4, 8Hz), 7. 52(1H, t, J=7. 8Hz), 7. 87(2H, m), 8. 57(1H, s), 8. 78(1H, d, J=2Hz)
47	4-pyridyl		87	61	0. 77~1. 84(13H, m), 2. 70(3H, s), 3. 17(4H, m), 4. 03(1H, m), 4. 20(1H, m), 4. 42(1H, ddd, J=5. 8Hzx3), 6. 42(1H, d, J=5Hz), 6. 49(1H, d, J=10Hz), 6. 89(1H, s), 7. 80(2H, m), 8. 81(2H, m)

EP 0 468 641 A2

Table 2 (continued)

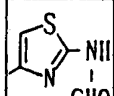
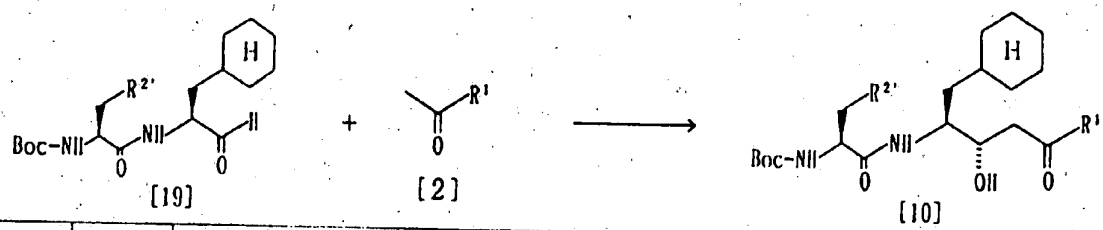
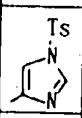
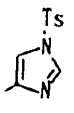
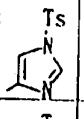
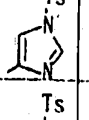
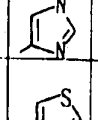
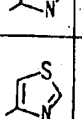
Compd. of Prep. No.	R^1	R^2	[9] Yield% (from [7])	[10] Yield%	[10] IR νmax cm^{-1} or NMR(δ)
48	phenyl		62	89	0.77~1.82(13H, m), 1.38(9H, s), 3.10(4H, m), 4.03(1H, m), 4.16(1H, m), 4.41(1H, t, J=5.2Hz), 6.71(1H, s), 6.89(1H, d, J=8.2Hz), 7.47(2H, t, J=7.8Hz), 7.59(1H, m), 7.94(2H, d, J=7.2Hz), 8.47(1H, s)
49	4-pyridyl	$-CONH_2$	86	65	0.76~1.82(13H, m), 1.41(9H, s), 2.67(2H, m), 3.06(1H, dd, J=4.2, 18Hz), 3.27(1H, dd, J=8.4, 18Hz), 4.04(1H, m), 4.24(1H, m), 4.37(1H, t, J=6.4Hz), 7.07(1H, d, J=9.4Hz), 7.85(2H, m), 8.76(2H, m)
50	4-pyridyl	-SMe	66	36	0.82~1.88(13H, m), 1.38(9H, s), 2.15(3H, s), 2.87(1H, dd, J=6.4, 13.6Hz), 2.95(1H, t, J=7.6Hz), 3.10(1H, dd, J=2.2, 18.8Hz), 3.42(1H, dd, J=9.4, 18.6Hz), 4.12(1H, m), 4.23(1H, ddd, J=6Hzx3), 4.28(1H, m), 5.37(1H, d, J=6Hz), 6.55(1H, d, J=10Hz), 7.77(2H, m), 8.82(2H, m)

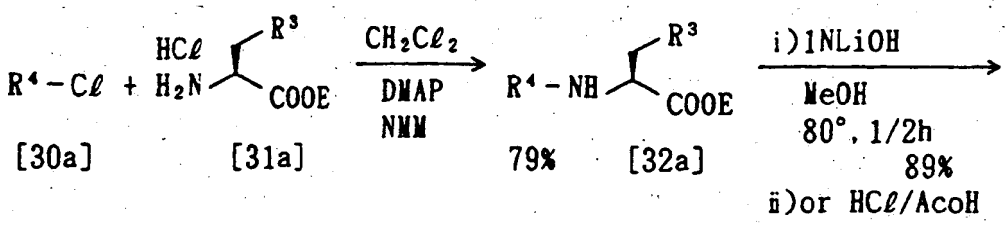
Table 3

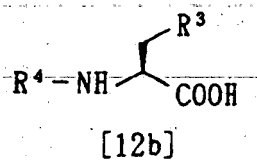


[19] + [2] → [10]

Compd. of Prep. No.	R1	R2'	Yield%	NMR δ (CDCℓ3)
51	p-methoxy-phenyl		10	0.75~1.94(13H, m), 1.33(9H, s), 2.44(3H, s), 3.00(2H, m), 3.08(2H, m), 3.88(3H, s), 4.01(1H, ddd, J=8.2Hz), 4.19(1H, m), 4.34(1H, ddd, J=6.4Hz), 6.12(1H, d, J=5.8Hz), 6.58(1H, d, J=9.8Hz), 6.93(2H, d, J=8.6Hz), 7.11(1H, s), 7.36(2H, d, J=8.2Hz), 7.81(2H, d, J=8.6Hz), 7.93(1H, s), 7.95(2H, d, J=9Hz)
52	3',4'-methylenedioxy-phenyl		19	0.77~1.83(13H, m), 1.34(9H, s), 2.44(3H, s), 3.00(4H, m), 4.00(1H, ddd, J=8.4, 8.4, 8.4Hz), 4.18(1H, d, J=6.2Hz), 4.32(1H, ddd, J=6Hz), 6.05(2H, s), 6.13(1H, m), 6.54(1H, d, J=9.8Hz), 6.85(1H, d, J=8.2Hz), 7.11(1H, d, J=0.4Hz), 7.36(2H, d, J=8.4Hz), 7.43(1H, d, J=1.4Hz), 7.58(1H, td, J=8.2.0.8Hz), 7.80(2H, d, J=8.4Hz), 7.92(1H, d, J=1.2Hz)
53	3-thienyl		23	Identical with those of compound in Ex. No. 27
54	morpholino-carbonyloxy-phenyl		27	0.72~2.00(13H, m), 1.34(9H, s), 2.44(3H, s), 3.00(2H, m), 3.10(2H, m), 3.52~3.8(8H, m), 4.00(1H, ddd, J=8Hz), 4.18(1H, m), 4.33(1H, ddd, J=6.6Hz), 6.10(1H, m), 6.58(1H, d, J=7Hz), 7.12(1H, d, J=3.4Hz), 7.36(3H, m), 7.47(1H, t, J=8Hz), 7.68(1H, m), 7.82(3H, m), 7.94(1H, d, J=1.4Hz)
55	phenyl		28	Identical with those of compound in Ex. No. 21
56	N-methyl-3-pyrrolyl		39	0.70~1.85(13H, m), 1.38(9H, S), 2.81(2H, d, J=5.6Hz), 3.20(1H, dd, J=4.8, 14.2Hz) 3.45(1H, dd, J=5.2, 14.8Hz), 3.69(3H, S), 3.92(1H, m), 4.07(1H, t, J=5.8Hz), 4.49(1H, ddd, J=6.8Hzx3) 6.48(1H, d, J=9.6Hz), 6.57(1H, S), 6.58(1H, S), 7.12(1H, d, J=2Hz), 7.32(1H, S), 8.77(1H, d, J=2Hz)
57	cyclohexyl		31	0.6~1.92(13H, m), 2.33(1H, m), 2.45~2.75(2H, m), 3.20(1H, dd, J=14.4, 5.2Hz) 3.44(1H, dd, J=14.8.3.8Hz), 3.85(1H, m), 3.93(1H, m), 4.45(1H, ddd, J=6.2.6.2.6.2Hz) 6.40(1H, d, J=9.8Hz), 6.49(1H, d, J=6.8Hz), 7.12(1H, d, J=1.6Hz), 8.78(1H, d, J=1.8Hz)

Preparation 58





R^3 = phenyl
R^4 = (N-morpholino)sulfonyol
E = CH_3

To a suspension of methyl ester of L-phenylalanine hydrochloride [31a] (4.31g, 20mmol) in dichloromethane (50ml) are added N-methylmorpholine (6.7g, 66mmol, 3.3eq). N-Morpholinosulfonyl chloride [30a] (4.44g, 24mmol, 1.2eq) in dichloromethane (4ml) and subsequently DMAP (244mg, 2.0mmol, 0.1eq) and the mixture is stirred overnight at room temperature. The reaction mixture is washed with 1N HCl and H_2O and the dichloromethane layer is dried over $MgSO_4$ and concentrated to dryness in vacuo. The residue is subjected to silica gel column chromatography (SiO_2: 110g, CH_2Cl_2:MeOH = 20:1) to obtain the compound [32a] (5.16g, 79%).

(i) To a solution of the compound [32a] (2.666g, 8.1mmol) in MeOH (12ml) is added 1N LiOH (12ml, 12mmol, 1.5eq) and the mixture is stirred at 80°C for 30 minutes. After removal of MeOH in vacuo, the reaction mixture is washed with ethyl acetate. The mixture is then treated with active carbon, adjusted to pH 2 - 3 with 1N HCl, and extracted with ethyl acetate. The extract is washed with saturated aqueous sodium chloride, dried over $MgSO_4$, and concentrated to dryness in vacuo. The residue is recrystallized from ethyl acetate/n-hexane to colorless needles of N-(N-morpholino)sulfonyl-phenylalanine [12b] (2.267g, 89%). m.p. 164 - 6°C (decomposition)

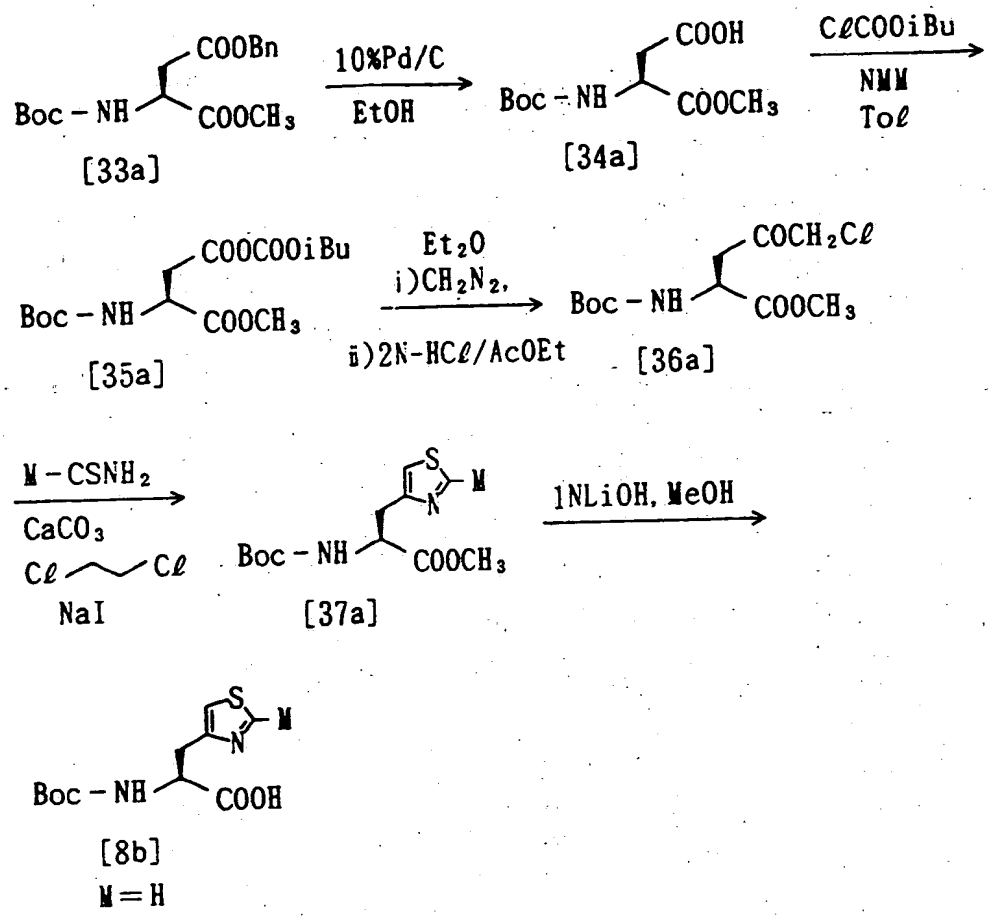
(ii) To the compound [32b] (E=Et) (920mg, 2.7mmol) are added 6N HCl (9.2ml) and acetic acid (2ml) and the mixture is heated with stirring on an oil bath of 100°C for one hour. After cooling, the reaction mixture is concentrated to dryness in vacuo. The residue is made alkaline by dissolving into saturated aqueous sodium bicarbonate. The aqueous solution is washed with dichloromethane (10ml x 3), treated with active carbon, and neutralized with 6N HCl. The solution is then made acidic up to pH 3 by addition of 10% aqueous citric acid and extracted with ethyl acetate (50ml x 3). The organic layer is washed with saturated aqueous sodium chloride (x 2), dried over $MgSO_4$, and concentrated to dryness in vacuo to give the compound [12c] as a crystalline residue (620mg, 74%). Recrystallization from dichloromethane/isopropyl ether affords white crystals (543mg, 64%). m.p. 157 - 158°C.

$[\alpha]_D$=-17.7±0.6°(C=1.0; MeOH; 25.0°C)

IRνmax(cm^{-1}): 3320, 3200-2600(br), 1750, 1603, 1585, 1500, 1455, 1400, 1352, 1300

NMR(δ): 2.93(5H,m), 3.17(1H,dd,J=5.2,14.2Hz), 3.54(4H,m), 4.11(1H,dd,J=5.2,8.6Hz), 7.30(5H,m)

Preparation 59



a) A solution of methyl ester of N-Boc-ω-benzyl-L-aspartic acid [33a] (52.7g, 0,156mmol) in a mixture of water (10ml), acetic acid (10ml) and methanol (150ml) is subjected to a catalytic reduction in the presence of 10% Pd-C (4.0g) under an atmosphere of hydrogen gas at room temperature. The reduction is conducted with stirring and under atmospheric pressure. After a 3-hour reaction, the catalyst is filtered off and the filtrate is evaporated to dryness in vacuo. The residue is dissolved in saturated aqueous sodium bicarbonate and the aqueous layer is washed with dichloromethane (50ml x 3), made acidic with citric acid (about pH3), and extracted with ethyl acetate (200ml x 4) while salting out with the addition of sodium chloride. The ethyl acetate layer is dried over $MgSO_4$ and concentrated to dryness in vacuo. Trituration of the residue with the addition of n-hexane affords the carboxylic acid [34a] (37.5g, 98%) as a white solid.

To a solution of the above product [34a] (18.8g, 76mmol) and N-methylmorpholine (7.8g, 77.1mmol, 1.0eq) in ethyl ether (200ml) is added isobutyl chlorocarbonate (9.92ml, 76.5mmol, 1.0eq) over 10 minutes at a temperature between -15°C and -10°C under nitrogen atmosphere, and the mixture is stirred at the same temperature for 30 minutes. Precepitated methylmorpholine hydrochloride is filtered off, and the filtrate is added to a solution of diazomethane in ethyl ether which has previously been prepared from nitrosomethylurea (37g, 359mmol) with stirring at -10°C over 5 minutes. After 2.5-hour stirring at room temperature, the mixture is concentrated in vacuo to remove excessive diazomethane. To the mixture is added ethyl acetate (150ml) and then dropwise added 2N HCl/ethyl acetate (45ml) at a temperature betwen -40°C and -30°C. After 30-minutes stirring, the mixture is neutralized with saturated aqueous sodium bicarbonate. The ethyl acetate layer is separated, dried over $MgSO_4$, evaporated to dryness in vacuo, and subjected to silica gel chromatography (SiO_2: 150g, AcOEt:CH_2Cl_2 = 6:1) to obtain the chloromethyl ketone [36a] (20.3g, 95%) as an oil.

To a solution of the above compound [36a] (40.3g, 144.1mmol) in MeCN (160ml) are added $CaCO_3$ (28g, 280mmol, 1.9eq) and thioformamide ($HCSNH_2$, 14g, 229.1mmol, 1.6eq) and the mixture is stirred at room temperatur for 18 hours under nitrogen atmosphere. Insoluble materials are filtered off and the filtrate is concentrated to dryness in vacuo. The residue is dissolved in dichloromethane, subsequently washed with 7% aqueous

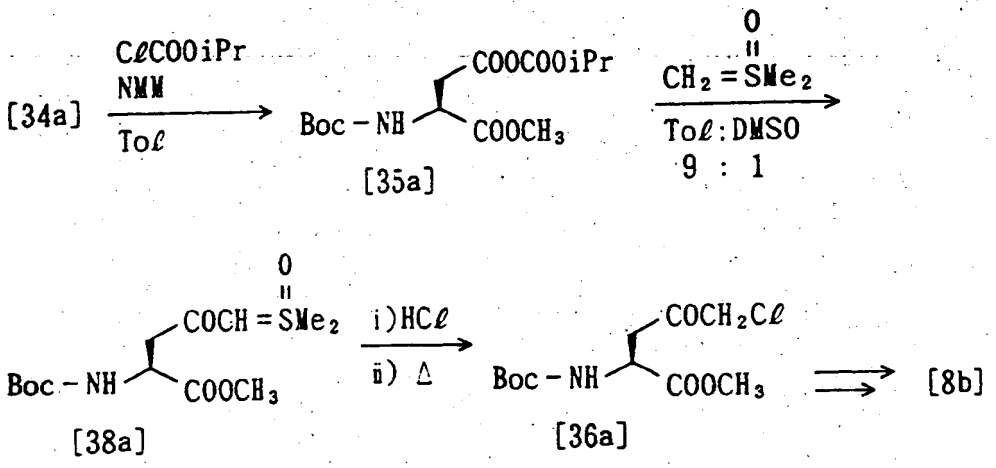
sodium bicarbonate, 1N NaOH, and water, two tim s each, to remove non-reacted thioformamide. The dichloromethane layer is dried over $MgSO_4$, concentrated to dryness in vacuo, and subjected to silica gel chromatography (SiO_2: 370g, M CN:CH_2Cl_2 = 1:7) to obtain (4-thiazolyl)alanine derivativ [37a] (29.15g, 71%) as an oil.

To the solution of above product [37a] (29.1g, 101.6mmol) in m thanol(120ml) is added 1N LiOH (112ml, 112mmol, 1.1eq) with stirring and ice-cooling and the mixture is stirred for ten minutes at the same temperature and allowed to react an additional one hour at room temperature. The reaction mixture is concentrated in vacuo on a water bath below 30°C to remove methanol and the residue is washed three times with dichloromethane. The aqueous layer is treated with active carbon, and citric acid to adjust the pH to 3, and extracted with ethyl acetate (150ml x 3). To the organic layer washed two times with saturated aqueous sodium chloride are added $MgSO_4$ and active carbon, the mixture is filtered and the filtrate is concentrated to dryness in vacuo to obtain crystalline crude product [8b] (26.96g, 97%). Recrystallization of the product from n-hexane provides pure product [8b] (26.2g, 95%). m.p. 96 - 98°C

$[\alpha]_D$=-4.2°(c=2; MeOH; 24°C)

NMR(δ): 1.47(9H,s), 3.41(1H,dd,J=5.6,14.6Hz), 3.56(1H,dd,J=3.4,11.0Hz), 4.59(1H,m), 3.60(1H,d,J=3.6Hz), 7.14(1H,d,J=2Hz), 8.94(1H,d,J=2Hz)

b)



i) Preparation of carbonic anhydride

To a solution of compound [34a] (500mg, 2.02mmol) and N-methylmorpholine (225mg, 2.22mmol, 1.1eq) in toluene (4ml) is added isopropyl chlorocarbonate (0.254ml, 2.22mmol, 1.1eq) with stirring at a temperature between -15°C and -10°C under nitrogen atmosphere and the mixture is stirred at the same temperature for one hour to separate out N-methylmorpholine hydrochloride.

ii) Preparation of Corey reagent (dimethylsulfoxonium methylide)

To a suspension of trimethylsulfoxonium iodide (1.024g, 4.65mmol) in toluene (9ml) and DMSO (1ml) is added potassium t-butoxide (522mg, 4.65mmol, 1.0eq) with stirring under nitrogen atmosphere, and the mixture is heated with stirring on an oil bath at 70 - 75°C for 30 minutes. Orange crystals turn to grayish white crystals.

The carbonic anhydride solution obtained in the above step i) is charged in a dropping funnel with a cotton stopper. The solution is dropwise added to the Corey reagent prepared in the step ii) from the funnel with stirring and ice-cooling under nitrogen atmosphere over 10 minutes and the mixture is stirred at room temperature for one hour. The mixture is filtered and the filtrate is extracted with water (10ml x 3). The aqueous layer is extracted with dichloromethane (10ml x 4). Each extract is washed with water, dried over $MgSO_4$, and concentrated to dryness in vacuo to obtain 600mg of crude product. Chromatography (SiO_2: 40g, 3.5% MeOH/CH_2Cl_2) of the crude product gives the aimed ylide compound [38a] (554mg, 85%) as an oil.

To a solution of the ylide [38a] (3.16g, 9.83mmol) in dichloroethane (26ml) is added 2N HCl/ethyl acetate (4.92ml, 9.84mmol) with stirring at -10°C and the mixture is stirred for one hour. The mixture is warmed on an oil bath of 100°C. Although precipitates (HCl addition product) separate out after two minutes, they redissolve after 3.5 minutes. When the solution becomes turbid after 6 minutes, the solution is cooled immediately to ter-

minate the reaction and the reaction mixture is subjected to silica gel chromatography (SiO_2: 15g, AcOEt:CH_2Cl_2 = 1:7) to obtain chloromethyl k tone [36a] (2.308g, 84%) as a crystal substanc .

A suspension of the above product [36a] (2.308g, 8.25mmol), $HCSNH_2$ (1.26g, 20.62mmol, 2.5 q) and $CaCO_3$ (2.475g, 24.75mmol, 3eq) in dichloroethane (23ml), is stirred at room t mperature for 15 hours under nitrogen atmosphere. After addition of NaI (62mg, 0.414mmol, 0.05eq), the mixture is stirred for an additional two hours. Insoluble materials are filtered off and washed with dichloromethane. The filtrate and washings are combined and subsequently washed with saturated aqueous sodium bicarbonate, 1N NaOH, and H_2O (x 2). Chromatographic treatment of the solution in the same manner as described in the foregoing process a) provides (4-thiazolyl)-L-alanine derivative [37a] (1.878g, 80%) as an oil.

To a solution of the above compound [37a] (3.16g, 11.04mmol) in methanol (6ml) is added with stirring and ice-cooling 1N LiOH (13ml, 13mmol, 1.18eq) and the mixture is stirred at room temperature for one hour. Similar procedure as disclosed in the process a) provides crude product [8b] (2.9g, 97%). Recrystallization of the product from ethyl ether/n-hexane gives pure product [8b] (2.6g, 88%) as colorless crystals. m.p. 110 - 112°C. $[\alpha]_D$=-4.8 (c=2.0; MeOH; 25°C)

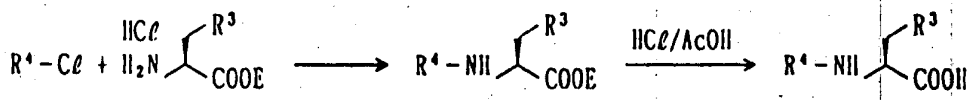
Preparation 60 and 61

N-sulfamylamino acids [12] listed in Table 4 are prepared from the compounds [30] in the same manner as disclosed in Preparation 58.

Preparation 62 and 63

2-Substituted (4-thiazolyl)-L-alanines [8] listed in Table 5 are prepared from the compounds [36] in the same manner as disclosed in Preparation 59.

Table 1



[30] [31] [32] [12]

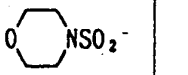
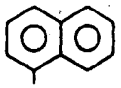
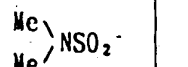
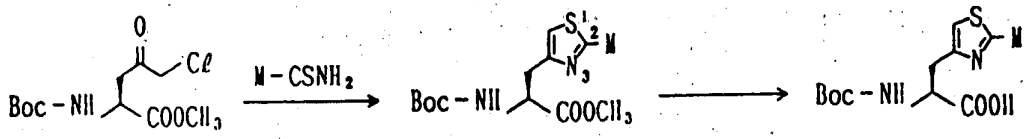
Compd. of Prep. No.	R^4	R^3	E	[32] Yield%	[10] Yield%	[10] $[\alpha]_D^{\circ}$ C=1, MeOH (Temp. ℃)	[10] IR $\nu_{max}^{CHCl_3}$ cm^{-1}	[10] NMR(δ)
60			Me	88	76	-56.7(25)	3480. 3340. 3200～2400. 1723(1750)1598. 1508. 1450. 1395. 1342. 1155. 1111. 1070. 848	2.55(2H. m). 2.63(2H. m). 3.13(2H. m). 3.20(3H. m). 3.55(1H. bs). 3.80(1H. dd. J=4.6. 14Hz). 4.35(1H. dt. J=4.4. 10Hz). 5.05(1H. d. J=10.2Hz). 7.37(2H. m). 7.57(2H. m). 7.89(2H. m). 8.10(1H. d. J=8.2Hz)
61			Et	82	26			2.58(6H. s). 2.98(1H. dd. J=7.8. 13.6Hz). 3.20(1H. dd. J=5.2. 13.6Hz). 4.24(1H. dofdd. J=9.6. 7.4. 4.6Hz). 4.90(1H. d. J=10Hz). 4.90(1H. bs). 7.30(5H. m)

Table 5



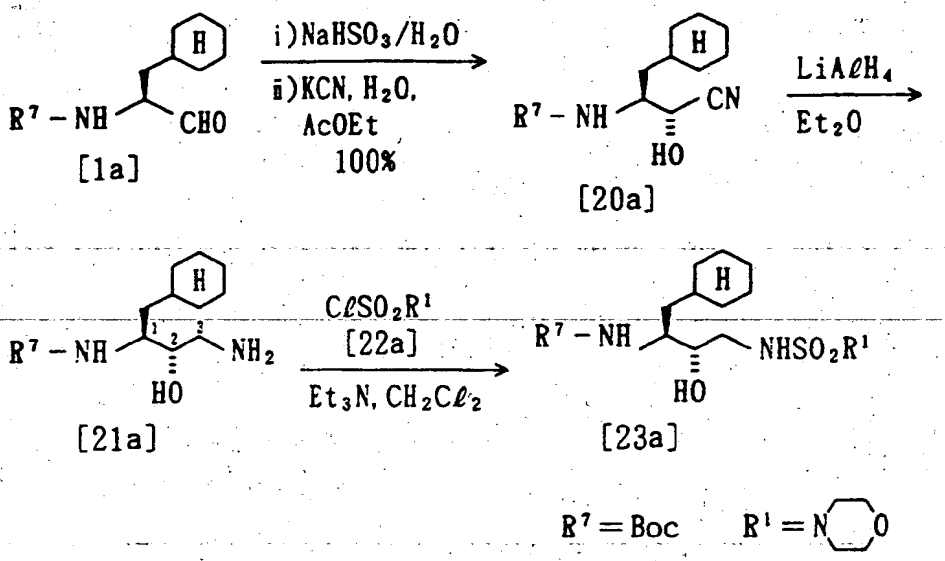
[36] [37] [8]

Compd. of Prep. No.	M	[37] Yield%	[37] $[\alpha]_D^{\circ}$ C=1, MeOH (temp. ℃)	[8] Yield%	[8] mp. (℃)	[8] $[\alpha]_D^{\circ}$ C=1, MeOH (temp. ℃)	[8] IR $\nu_{max}^{CHCl_3}$ cm^{-1}	[8] NMR(δ)
62	CH_3	42	—	93	135-136	(C=2) -20.4 (24)	3430. 2440(br) 1700. 1495. 1435. 1392 1368. 1160 1060	
63	NH_2	88	-345 (24) -10.1* (22)	* 87	* 156-157	* -4.3 (22)	*3440. 3200. 2440(br) 1700. 1565. 1500 1455. 1435. 1392 1370. 1160 1062	*1.50(9H, s). 3.38(2H, m). 4.64(1H, m). 5.15(2H, d, J=6.8Hz). 6.69(1H, s). 8.48(1H, s)

* formyl compound

EP 0 468 641 A2

Preparation 64



To the aldehyde compound [1a] (10.08g, 39.5mmol) is added $NaHSO_3$ (10.08g) in water (70ml) and the mixture is stirred with ice-cooling for 16 hours. The resultant solution is stirred at room temperature for 4 hours after addition of KCN (6.3g) in water (16.8ml) and ethyl acetate (137ml). The ethyl acetate layer is separated from the reaction mixture, washed with saturated aqueous sodium chloride, dried, and concentrated. The residue is subjected to column chromatography using Lobar column Size C (CH_2Cl_2:acetone = 19:1). Resultant product is recrystallized from hexane to give the aimed product [20a] (6.51g, 58%).

The product [20a] (3.56g, 12.6mmol) in anhydrous THF (50ml) is added dropwise to a suspension of $LiAlH_4$ (574mg, 1.2mol) in anhydrous THF (30ml) with stirring and ice-cooling over 30 minutes. The mixture is stirred at 0°C for an additional one hour. A small amount of ethyl acetate and ice water are added to the mixture to separate out inorganic materials. The insoluble materials are filtered, and the filtrate is concentrated in vacuo and then purified with silica gel chromatography (SiO_2: 120g, CH_2Cl_2:MeOH:NH_4OH = 80:20:2). The aimed compound [21a] (2.21g, 61%) is thus obtained.

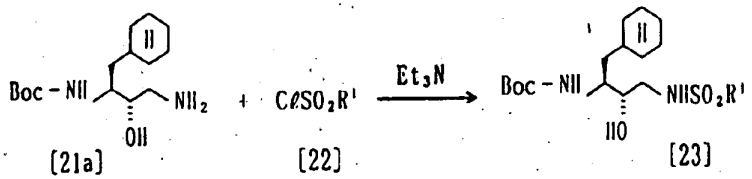
To a solution of the compound [21a] (12.49g, 43.6mmol) in anhydrous dichloromethane (200ml) are added triethylamine (8.8g, 2.0eq) and morpholinosulfonyl chloride (10.1g, 1.25eq) and the mixture is stirred at room temperature for 3 hours and concentrated in vacuo. The residue is dissolved in ethyl acetate, washed with water, dried, and evaporated to remove the solvent. The residue is purified with silica gel chromatography (SiO_2: 200g, CH_2Cl_2:MeOH:NH_4OH = 90:10:1). The aimed compound [23a] (18.16g, 95%) is thus obtained.

NMR(δ): 0.70-1.85(13H,m), 1.45(9H,s), 3.02(1H,m), 3.18(5H,m), 3.72(6H,m), 4.62(1H,d,J=9.2Hz), 5.58(1H,bt)

Preparation 65-74

The compounds [23] listed in Table 6 are prepared in the manner as taught in Preparation 64.

Table 6



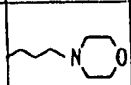
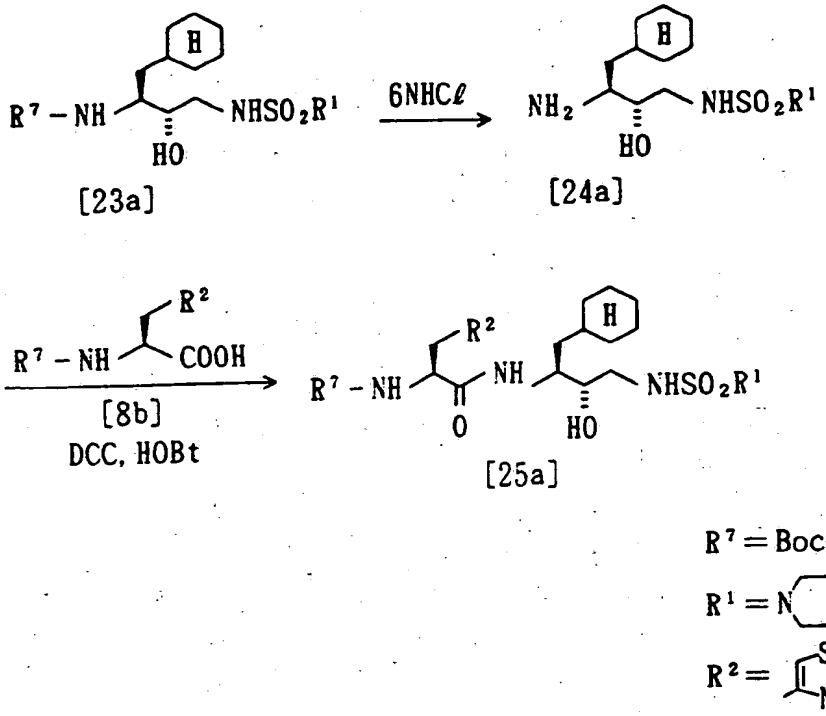
Compd. of Prep. No.	R'	[23] yield %	[23] NMR(δ)
65	-NMe2	97	0.80~1.90(13H, m), 1.45(9H, s), 2.80(6H, s), 3.08(2H, m), 3.72(2H, m), 4.63(1H, d, J=9.2Hz), 5.48(1H, m)
66		90	0.70~1.80(13H, m), 1.37(9H, s), 2.49(1H, bs), 2.82(1H, dt, J=6.2, 13.5Hz), 3.12(1H, dt, J=7, 13Hz), 3.68(2H, m), 4.60(1H, d, J=9.3Hz), 4.47(1H, dd, J=4.6Hz), 8.17(1H, m), 8.79(1H, bd), 9.08(1H, bs)
67		93	0.70~1.85(13H, m), 1.39(9H, s), 2.90(1H, dt, J=6.1, 13.4Hz), 3.16(1H, dt, J=7.0, 12.9Hz), 2.60(1H, m), 3.67(2H, m), 4.57(1H, d, J=9.2), 5.89(1H, t, J=7Hz), 7.07(1H, dd, J=3.7, 5.0Hz), 7.60(2H, m), 6.24(1H, bt)
68		99	0.65~1.80(13H, m), 1.32(9H, s), 2.89(2H, bt), 3.55(1H, m), 3.66(1H, m), 4.58(1H, d, J=9.2Hz), 6.80(1H, bt), 7.57(1H, dd, J=4.4, 8.4Hz), 7.66(1H, t, J=7.4Hz), 8.07(1H, dd, J=1.0, 8.2Hz), 8.29(1H, dd, J=1.6, 8.4Hz), 8.42(1H, dd, J=1.4, 7.4Hz), 9.05(1H, dd, J=1.6, 4.4Hz)
69		97	0.70~1.80(13H, m), 1.37(9H, s), 2.58(1H, bd, J=5Hz), 2.80(1H, dt, J=6.2, 13.6Hz), 3.08(1H, dt, J=6.5, 13.6Hz), 3.65(2H, m), 4.56(1H, d, J=9.2Hz), 5.82(1H, bt, J=6Hz), 7.53(3H, m), 7.85(2H, m)
70		72	0.75~1.87(13H, m), 1.45(9H, s), 1.98(1H, bs), 2.52(4H, m), 2.86(2H, m), 3.17(4H, m), 3.73(6H, m), 4.62(1H, d, J=9.4Hz), 5.63(1H, bt)
71		36	0.75~1.88(13H, m), 1.45(9H, s), 2.03(2H, m), 2.49(6H, m), 3.13(4H, m), 3.72(6H, m), 4.65(1H, d, J=9.1Hz), 5.82(1H, bt)

Table 6 (continued)

Compd. of Prep. No.	R'	[23] yield %	NMR(δ)
72	~NMe$_2$	75	0.75~1.90(13H, m), 1.44(9H, s), 2.29(6H, s), 2.80(2H, m), 3.16(5H, m), 3.64(2H, m), 4.66(1H, d, J=9.6Hz)
73	Me	97	0.75~1.85(13H, m), 1.45(9H, s), 2.85(1H, bs), 2.96(3H, s), 3.14(2H, m), 3.72(2H, m), 4.65(1H, d, J=9.4Hz), 5.53(1H, bt)
74	~	98	0.94(3H, t, J=7.2Hz), 0.80~1.95(17H, m), 1.45(9H, s), 2.76(1H, bs), 3.00(2H, m), 3.16(2H, m), 3.70(2H, m), 4.63(1H, d, J=9Hz), 5.44(1H, t, J=7Hz)

Preparation 75



A mixture of the compound [23a] (18.16g, 41.6mmol), THF (150ml), and 6N HCl (150ml) is stirred at room temperature for 4 hours. The reaction mixture is made alkaline with Na_2CO_3 and saturated aqueous $NaHCO_3$ and extracted with a mixture of dichloromethane and methanol (9:1). The organic layer is dried and evaporated to dryness in vacuo. The residue is subjected to silica gel column chromatography (SiO_2: 100g, CH_2Cl_2:MeOH:NH_4OH = 80:20:2). The compound [24a] (14.0g, quantitative amount) is thus obtained.

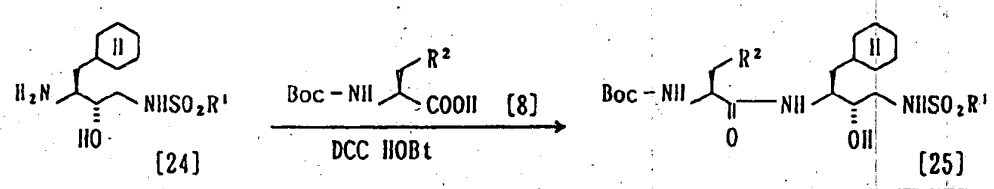
To a solution of the above compound [24a] (14.0g, 41.6mmol) in acetonitrile (200ml) are added 4-thiazolyl-L-alanine [8b] (12.09g, 1.1eq) and HOBt (7.04g, 1.25eq) with ice-cooling. To the mixture is added DCC (11.18g, 1.3eq) and the resulting mixture is stirred for one hour at 0 °C and one hour at room temperature. The reaction mixture is filtered after addition of ethyl acetate and the filtrate is concentrated in vacuo. The residue is subjected to silica gel column chromatography (SiO_2: 600g, CH_2Cl_2:MeOH:NH_4OH = 90:10:1) to give the product [25a] (24.5g, quantitative amount).

NMR(δ): 0.70-1.80(13H,m), 1.45(9H,s), 2.45(1H,bs), 2.98(2H,m), 3.18(4H,m), 3.30(2H,m), 3.75(5H,m), 4.02(1H,m), 4.46(1H,ddd,J=6.4Hx3), 5.72(1H,bt,J=6.6Hz), 6.16(1H,d,J=6.4Hz), 6.36(1H,d,J=9.2Hz), 7.15(1H,d,J=1.8Hz), 8.82(1H,d,J=2Hz)

Preparation 76-86

Compounds [25] listed in Table 7 are prepared according to the procedure disclosed in Preparation 75.

Table 7



Compd. of Prep. No.	R¹	R²	[25] Yield%	[25] NMR(δ)
76	-NMe₂		90	0.70~1.80(13H, m), 1.45(9H, s), 2.79(6H, s), 2.95(2H, m), 3.29(2H, m), 3.73(1H, m), 4.01(1H, m), 4.48(1H, ddd, J=6.6Hz), 5.58(1H, bt), 6.15(1H, d, J=7Hz), 6.39(1H, d, J=10Hz), 7.15(1H, d, J=1.8Hz), 8.82(1H, d, J=2Hz)
77			94	0.65~1.75(13H, m), 1.39(9H, s), 2.80(1H, dt, J=6.4, 13.6Hz), 3.00(1H, dt, J=6.6, 13.7Hz), 3.19(2H, d, J=5.6Hz), 3.70(1H, dt, J=2.3, 6.7Hz), 3.99(1H, m), 4.46(1H, ddd, J=6Hz), 6.05(1H, d, J=6.3Hz), 6.55(2H, m), 7.11(1H, d, J=1.8Hz), 7.45(1H, m), 7.80(1H, dd, J=4, 24Hz), 8.20(1H, d, J=7Hz), 8.77(1H, d, J=2Hz), 9.08(1H, bs)
78			99	0.65~2.00(13H, m), 1.43(9H, s), 2.81(1H, dt, J=6.3, 13.5Hz), 2.99(1H, dt, J=6.9, 13.5Hz), 3.24(2H, m), 3.66(1H, dd, J=2.4, 6.8Hz), 3.97(1H, m), 4.45(1H, ddd, J=6.5Hzx3), 6.02(1H, d, J=6.9Hz), 6.22(1H, bt), 6.39(1H, d, J=9.3Hz), 7.10(2H, m), 7.58(2H, m), 8.75(1H, d, J=1.8Hz)
79			96	0.55(13H, m), 1.43(9H, s), 2.79(2H, m), 3.11(1H, dd, J=5.7, 14.7Hz), 3.22(1H, dd, J=5.4, 14.7Hz), 3.65(1H, m), 3.84(1H, m), 4.32(1H, ddd, J=6.6Hzx3), 6.09(1H, d, J=6Hz), 6.27(1H, d, J=9.4Hz), 6.78(1H, t, J=6.2Hz), 7.02(1H, d, J=1.8Hz), 7.56(1H, dd, J=4.3, 8.4Hz), 7.65(1H, t, J=7.4Hz), 8.06(1H, dd, J=1.4, 8.3Hz), 8.27(1H, dd, J=1.8, 8.4Hz), 8.41(1H, dd, J=1.4, 7.3Hz), 8.69(1H, d, J=1.9Hz), 9.04(1H, dd, J=1.7, 4.2Hz)

Table 7 (continued)

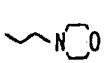
Compd. of Prep. No.	R^1	R^2	[25] Yield%	[25] NMR(δ)
80			99	0.67~2.00(13H, m), 1.43(9H, s), 2.74(1H, dt, J=6.9, 13.5Hz), 2.94(1H, dt, J=6.8, 13.5Hz), 3.18(1H, dd, J=6.3, 14Hz), 3.27(1H, dd, J=5.7, 14Hz), 3.62(1H, dt, J=2.6, 6.8Hz), 3.95(1H, m), 4.41(1H, ddd, J=6.6Hzx3), 5.95(1H, bt), 6.05(1H, d, J=6.8), 6.29(1H, d, J=9.3Hz), 7.07(1H, d, J=1.9Hz), 7.52(3H, m), 7.86(2H, m), 8.73(1H, d, J=2.0Hz)
81			99	0.63~1.78(13H, m), 1.45(9H, s), 2.14(1H, bs), 2.52(4H, bt, J=4.6Hz), 2.86(2H, t, J=7Hz), 3.05(2H, bt, J=6Hz), 3.14~3.40(4H, m), 3.66(1H, m), 3.73(4H, m), 4.00(1H, m), 4.42(1H, ddd, J=6.2Hz), 5.80(1H, bt), 6.24(1H, d, J=6.6Hz), 6.31(1H, d, J=9.4Hz), 7.14(1H, d, J=2Hz), 8.81(1H, d, J=2Hz)
82			99	0.70~1.80(13H, m), 1.45(9H, s), 2.01(2H, m), 2.49(6H, m), 3.08(4H, m), 3.30(2H, m), 3.72(5H, m), 4.00(1H, m), 4.43(1H, ddd, J=6.6Hzx3), 5.88(1H, bt), 6.24(1H, d, J=6.6Hz), 6.52(1H, d, J=9.6Hz), 7.15(1H, d, J=1.8Hz), 8.82(1H, d, J=1.8Hz)
83			77	0.60~1.80(13H, m), 1.45(9H, s), 2.29(6H, s), 2.81(2H, t, J=6.2Hz), 3.04(2H, d, J=6.6Hz), 3.18(2H, m), 3.25(1H, dd, J=5.6, 14.6Hz), 3.34(1H, dd, J=5.4, 14.6Hz), 3.65(1H, dt, J=2.4, 6.2Hz), 3.98(1H, m), 4.45(1H, ddd, J=6.6Hz), 6.22(1H, d, J=6.6Hz), 6.40(1H, d, J=9.6Hz), 7.14(1H, d, J=2Hz), 8.81(1H, d, J=2Hz)
84	Me		75	0.70~1.80(13H, m), 1.45(9H, s), 2.96(6H, s), 3.03(2H, m), 3.30(2H, m), 3.70(1H, m), 4.02(1H, m), 4.46(1H, ddd, J=6.6Hzx3), 5.72(1H, bt), 6.21(1H, d, J=6.6Hz), 6.39(1H, d, J=9.6Hz), 7.15(1H, d, J=1.6Hz), 8.82(1H, d, J=1.8Hz)
85			83	0.95(3H, t, J=7.2Hz), 0.65~1.88(17H, m), 1.45(9H, s), 3.00(5H, m), 3.30(2H, m), 3.68(1H, dt, J=2.3, 6.6Hz), 4.01(1H, m), 4.45(1H, ddd, J=6.2Hzx3), 5.56(1H, bt), 6.18(1H, d, J=6.6Hz)6.35(1H, d, J=9.6Hz), 7.14(1H, d, J=1.8Hz), 8.81(1H, d, J=2.0Hz)

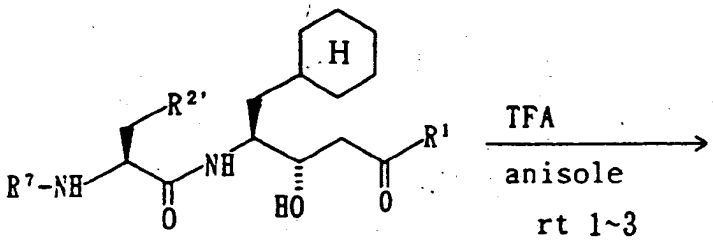
Table 7 (continued)

Compd. of Prep. No.	R¹	R²	[25] Yield%	NMR(δ)
86			99	0.65~1.75(13H, m), 1.43(9H, s), 2.64(3H, s), 2.74(1H, dt, J=6.3, 13.6Hz), 2.96(1H, dt, J=6.8, 13.4Hz), 3.10(2H, m), 3.61(1H, dt, J=3.6.6Hz), 3.96(1H, m), 4.34(1H, ddd, J=5.8Hz), 5.90(1H, m), 6.00(1H, d, J=6.2Hz), 6.32(1H, d, J=9.2Hz), 6.82(1H, s), 7.52(3H, m), 7.86(2H, dd, J=1.6, 7.8Hz)

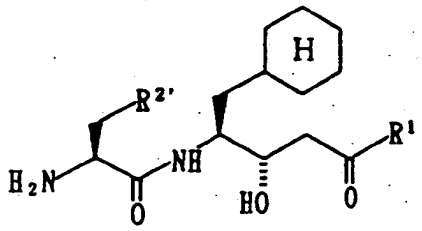
Example 1

3-t-Butylsulfonyl-2(S)-phenylmethylpropionyl-His-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(4-pyridyl)butylamide [Ia]

1) His(Ts)-1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(4-pyridyl)butylamide [11a]



[10a]



[11a] $R^1 = 4-$pyridyl

$R^1 = 4-$pyridyl
$R^{2'} = 4-$tosylimidazolyl
R^7 : Boc

Boc-His(Ts) 1(S)-cyclohexylmethyl-2(S), hydroxy-4-oxo-4-(4-pyridyl)butylamide [10a] (1.31g, 1.96mmol) prepared in Preparation 21 is dissolved in anisole (13ml). To the solution is added trifluoroacetic acid (13ml) with stirring and ice-cooling and the mixture is stirred at room temperature for one hour. After evaporation of the reaction mixture to dryness in vacuo, ice is added to the residue and the mixture is washed with ethyl ether. The aqueous layer neutralized with 3N NaOH and adjusted to pH8 by addition of powdered Na_2CO_3 is extracted with dichloromethane three times and finally extracted with a mixture of dichloromethane and methanol (10:1). The organic layer is washed with saturated aqueous sodium chloride, dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue is purified with silica gel chromatography (CH_2Cl_2:MeOH = 95:5) to obtain the aimed crude product (850mg, 73%). Recrystallization of the crude product from ethyl acetate provides the title compound [11a] (750mg, 65%) as a needle crystal. m.p.161-162°C

NMR(δ): 0.75-1.80(13H,m), 1.98(1H,br.s), 2.44(3H,s), 2.73(1H,dd,J=14.8,8.2Hz), 2.95~3.24(3H,m), 3.65(1H, dd,J=8.4,4.2Hz), 4.02(1H,m), 4.27(1H,m), 7.12(1H,d,J=1.2Hz), 7.36(2H,d,J=7.8Hz), 7.53(1H,d,J=10Hz), 7.70 (2H,m), 7.81(2H,d,J=8.4Hz), 7.92(1H,d,J=1.4Hz), 8.79(2H,m)

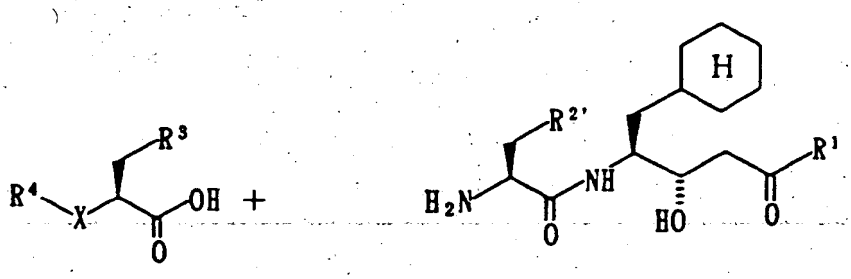
IR νmax($CHCl_3$)cm^{-1}:3680, 3340, 1690, 1654, 1602, 1593, 1515, 1475, 1450

Elemental analysis(as $C_{29}H_{39}N_5O_6S$)

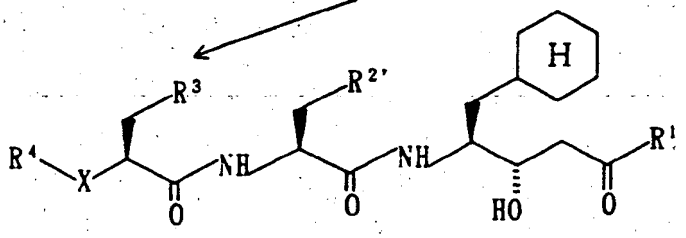
Calcd.: C:59.01; H:6.75; N:11.87; S:5.43

Found : C:59.12; H:6.69; N:11.68; S:5.21

2) 3-t-Butylsulfonyl-2(S)-ph nylm thylpropionyl-His(Ts) 1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(4-pyridyl)butylamide [13a]



[12a] [11a]

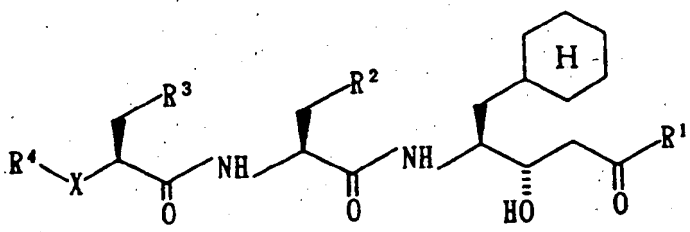


[13a]

R^4 = t-butylsulfonyl
R^3 = phenyl
X = CH_2
R^1 = 4-pyridyl
$R^{2'}$ = 1-tosyl-4-imidazolyl

To a solution of the ketone compound [11a] (334mg, 0.57mmol) in dichloromethane (1ml) are added 3-t-butylsulfonyl-2(S)-phenylmethylpropionic acid (220mg, 0.76mmol, 1.3eq), N-methylmorpholine (77mg, 0.76mmol, 1.3eq), and then DEPC (124mg, 0.76mmol, 1.3eq) and the mixture is stirred at room temperature for four hours. The reaction mixture is evaporated to dryness in vacuo and subjected to silica gel chromatography (CH_2Cl_2:MeOH = 95:5) to obtain the title compound [13a] (418mg, 89%) as colorless powders.
NMR δ: 0.70-2.10(14H,m), 1.33(9H,s), 2.43(3H,s), 2.70 -3.28(8H,m), 3.45(1H,dd,J=12.9,9.4Hz), 4.00(1H,m), 4.18(1H,m), 4.53(1H,ddd,J=5.8,5.8,5.8Hz), 6.34(1H,d,J=10Hz), 7.17(1H,d,J=1.2Hz), 7.22(5H,m), 7.34 (2H, d, J=8.4Hz), 7.81(2H,d,J=8.5Hz), 7.85(1H,d,J=1.2Hz), 7.75(2H,d,J=6.0Hz), 8.81(2H,d,J=5.9Hz)
IR νmax($CHCl_3$) cm^{-1}:3680, 3470, 3370, 1665, 1600, 1520, 1450, 1172, 1112, 1075

3) 3-t-Butylsulfonyl-2(S)-phenylmethylpropionyl-His 1(S)-cyclohexylmethyl-2(S)-hydroxy-4-oxo-4-(4-pyridyl) butylamide [Ia]



[Ia]

R^4 = t-butylsulfonyl
X = CH_2
R^1 = 4-pyridyl
R^2 = 4-imidazolyl
R^3 = phenyl

To a solution of the protected compound [13a] (740mg, 0.89mmol) obtained in the above step 2) in DMF (4ml) is added pyridinium hydrochloride (1030mg, 8.87mmol, 10.0eq) and th mixtur is stirred at room temperature for two hours. The reaction mixture is adjusted to pH 7 - 8 by addition of ice and 4% aqueous $NaHCO_3$ and extracted thre times with dichloromethane. The organic layer is washed with saturated aqueous sodium chloride, dried over $MgSO_4$, and concentrated to dryness in vacuo. The r sidue is purified with silica gel chromatography (CH_2Cl_2:MeOH:concNH_4OH = 950:50:1) to obtain the title compound [Ia] (543mg, 90%). Trituration of the residue with diisopropyl ether gives colorless powders.

NMR δ: 0.67-1.83(13H,m), 1.33(9H,s), 2.86(1H,d,J=13.5,8.4Hz), 2.97(1H,dd,J=13.0,9.8Hz), 3.10(5H,m), 3.26(1H,m), 3.56(1H,dd,J=13.0,9.8Hz), 4.02(1H,m), 4.20(1H,m), 4.56(1H,ddd,J=6.3,6.3,6.3Hz), 6.44 (1H, d, J=10Hz), 6.90(1H,s), 7.24(4H,m), 7.48(1H,s), 7.46(1H,bs), 7.70(2H,m), 8.78(2H,m)

$[\alpha]_D$=-22.5°(C=1.0; MeOH; 23°C) IR νmax($CHCl_3$)cm^{-1}:3460, 3360(br), 1662(1690sh), 1603, 1496, 1450, 1410, 1115

Elemental analysis (as $C_{36}H_{49}N_5O_6S.3/4H_2O$)

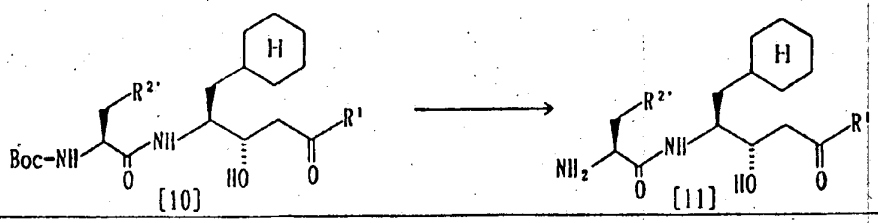
Calcd.: C:62.36; H:7.34; N:10.10; S:4.62

Found : C:62.42; H:7.33; N:10.21; S:4.49

Examples 2-52

The same procedure as disclosed in the steps 1) and 2) in Example 1 is repeated using, as the starting material, the compounds [10] prepared in foregoing Preparations 21-58, and the compounds [11] and [13] listed in Tables 8 (compound [11]) and 9 (compound [13]) are obtained. The compounds [13] (for example, compound [13] of No. 23) wherein R^1 or R^2 is not protected correspond to the compounds (I) of the invention. Where the substituent R^2 is protected, the compounds [13] are deprotected according to the procedure as disclosed in Step 3) in Example 1 to obtain the final products (I), which are listed in the following Table 10.

Table 8



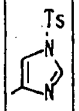
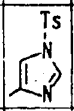
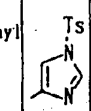
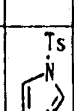
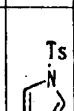
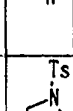
Comp. of Ex. No.	R1	R2'	[11] Yield% m.p. (℃)	[α]D°(C=1.0, CHCl3) (℃)	IR νmax cm-1 or NMR (δ)	Elemental analysis Calcd.	Found
2	phenyl		81 126-127	-49.1 (23.5)	3560, 3360, 1666, 1598, 1580, 1511 1450, 1382, 1172, 1075	C:63.58 H: 6.76 N: 9.89 S: 5.66	C:63.34 H: 6.67 N: 9.84 S: 5.67
3	o-fluorophenyl		67		3600, 3460(br), 1670, 1610, 1598, 1510, 1480, 1450, 1383, 1170, 1075	oil	
4	m-methoxyphenyl		55		0.70~1.83(13H, m), 2.05(3H, bs), 2.44(3H, s), 2.72(1H, dd, J=8, 16Hz), 2.98(1H, dd, J=10, 18Hz), 3.07(1H, dd, J=6, 16Hz), 3.18(1H, dd, J=3, 18Hz) 4.66(1H, dd, J=4, 8Hz), 3.85(3H, s), 4.02(1H, m), 4.24(1H, m), 7.17(1H, s) 7.17(1H, m), 7.30~7.60(3H, m), 7.35(2H, d, J=8.0Hz), 7.80(2H, d, J=8.4Hz), 7.91(1H, d, J=1.4Hz)	oil	
5	p-methylphenyl		43		3360, 1668, 1608, 1570, 1510, 1450, 1385, 1172, 1092, 1075	oil	
6	2,4-difluoro-phenyl		71	-43.9 (23.5)	3580, 3360, 1665, 1612, 1595, 1510, 1498, 1475, 1383, 1172, 1075, 970	C:59.78 H: 6.02 N: 9.30 S: 5.32 F: 6.31	C:59.53 H: 6.04 N: 9.42 S: 5.56 F: 6.38
7	1-naphthyl		49		3400(br), 1665, 1599, 1575, 1510, 1450, 1386, 1190, 1174, 1094, 1080, 909	oil	

Table 8 (continued)

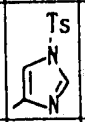
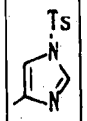
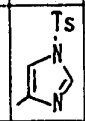
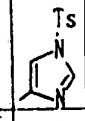
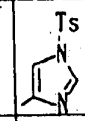
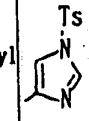
Compd. of Ex. No.	R^1	$R^{2'}$	[11] Yield%	[11] $[\alpha]_D^{*}$ (C=1.0, $CHCl_3$)(℃)	[11] mp(℃)	IR νmax cm^{-1} or NMR(δ)
8	3-thienyl		70			3680, 3360(br), 3120, 1665, 1598, 1510, 1475, 1450, 1382, 1172, 1076
9	2-thiazolyl		52			0.73~1.83(13H, m), 2.33(2H, bs), 2.44(3H, s), 2.76(1H, dd, J=7, 15Hz), 3.07(1H, dd, J=3.6, 14.6Hz), 3.18~3.38(2H, m), 3.68(1H, m), 4.02(1H, m), 4.25(1H, m), 7.14(1H, s), 7.35(2H, d, J=8.0Hz), 7.51(1H, d, J=9.0Hz), 7.69(1H, d, J=3.0Hz), 7.80(2H, d, J=8.4Hz), 7.95(1H, d, J=1.2Hz), 8.01(1H, d, J=3.0Hz)
10	m-fluorophenyl		66			3360, 1670, 1590, 1510, 1445, 1382, 1170, 1090, 1075
11	p-fluorophenyl		57	-45.8 (24.0)	128~130	3360, 3500(br), 1665, 1600, 1508, 1475, 1450, 1095, 1075
12	2,6-difluoro-phenyl		53	-23.9 (24.0)		3368, 1698, 1665, 1624, 1598, 1512, 1420, 1385, 1279, 1190, 1174, 1094, 1077, 1018
13	o-methoxyphenyl		25			0.70~1.85(13H, m), 2.20(3H, bs), 2.44(3H, s), 2.74(1H, dd, J=8, 15Hz), 2.95(1H, dd, J=10, 17Hz), 3.10(1H, dd, J=15.5Hz), 3.26(1H, dd, J=17, 3Hz) 3.69(1H, dd, J=5, 10Hz), 3.88(3H, s), 3.99(1H, m), 4.18(1H, m), 6.98(2H, m), 7.12(1H, s), 7.35(2H, d, J=8Hz), 7.50(1H, m), 7.72(1H, dd, J=7.5, 2Hz), 7.81(2H, d, J=8Hz), 7.92(1H, s)

Table 8 (continued)

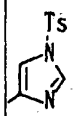
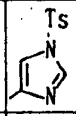
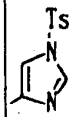
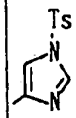
Compd. of Ex. No.	R^1	$R^{2'}$	[11] Yield%	mp(℃)	IR νmax cm^{-1} or NMR(δ)
14	o-chlorophenyl		75		0.70~1.82(13H, m), 2.40(3H, s), 2.44(3H, s), 2.72(1H, dd, J=8, 15.8Hz), 3.00(1H, dd, J=17.5, 10Hz), 3.07(1H, dd, J=15.5Hz), 3.17(1H, dd, J=17.5, 4Hz), 3.65(1H, dd, J=10, 5Hz), 3.98(1H, m), 4.23(1H, m), 7.11(1H, s), 7.25~7.58(6H, m), 7.81(2H, d, J=8.4Hz), 7.91(1H, d, J=1.4Hz)
15	m-cyanophenyl		79		3360, 2236, 1666, 1514, 1498, 1450, 1386, 1189, 1174, 1094, 1078, 909
16	o-methyl-sulfonyl-aminophenyl		38		3368, 1657, 1607, 1578, 1496, 1452, 1386, 1340, 1189, 1173, 1094, 1078, 968, 909
17	p-trifluoro-methylphenyl		53	113~115	3360, 1670, 1600, 1510, 1450, 1410, 1385, 1325, 1180, 1135, 1065

Table 8 (continued)

Compd. of Ex. No.	R¹	R²	[11] Yield%	[11] NMR (δ)
18	p-morpholinocarbonyloxyphenyl		81	0.73~2.20(13H, m), 2.44(3H, s), 2.75(1H, dd, J=14.8.8.6Hz), 2.93~3.24(3H, m), 3.5~3.82(8H, m), 4.02(1H, m), 4.23(1H, m), 7.13(1H, d, J=1.0Hz), 7.35(2H, d, J=8.0Hz), 7.35(1H, m), 7.47(1H, t, J=7.5Hz), 7.60(1H, d, J=10Hz), 7.67(1H, m), 7.81(2H, d, J=8.4Hz), 7.81(1H, m), 7.91(1H, d, J=1.4Hz)
19	p-morpholinocarbonylphenyl		41	0.70~1.85(13H, m), 2.28(3H, bs), 2.44(3H, s), 2.75(1H, dd, J=8.6.14.8Hz), 2.95~3.27(3H, m), 3.30~3.94(8H, m), 3.68(1H, dd, J=8.4.4.2Hz), 4.02(1H, m), 4.26(1H, m), 7.14(1H, d, J=1.4Hz), 7.36(2H, d, J=8Hz), 7.47~7.69(2H, m), 7.81(2H, d, J=8.4Hz), 7.93(1H, d, J=1.2Hz), 7.98(1H, d, J=1.6Hz), 8.00(1H, m)
20	3,4-methylenedioxyphenyl		74	0.70~2.15(13H, m), 2.44(3H, s), 2.73(1H, dd, J=14.4.8.4Hz), 2.91(1H, dd, J=17.8.9.6Hz), 3.09(1H, dd, J=14.6.4.2Hz), 3.13(1H, dd, J=18.4Hz), 3.67(1H, dd, J=8.6.3.8Hz), 4.00(1H, m), 4.20(1H, m), 6.05(2H, s), 6.84(1H, d, J=8.2Hz), 7.12(1H, d, J=1.0Hz), 7.36(2H, d, J=8.0Hz), 7.40(1H, d, J=1.6Hz), 7.53(1H, dd, J=8.2.1.6Hz), 7.81(2H, d, J=8.2Hz), 7.92(1H, d, J=1.4Hz)
21	cyclohexyl		68	0.70~1.89(23H, m), 2.13(3H, bs), 2.33(1H, m), 2.45(1H, m), 2.47(1H, dd, J=17.6.9.4Hz), 2.66(1H, dd, J=15.2.6Hz), 2.71(1H, dd, J=14.9.4Hz), 3.07(1H, dd, J=14.8.3.6Hz), 7.12(1H, d, J=1.2Hz), 7.37(2H, d, J=8.4Hz), 7.48(1H, d, J=10Hz), 7.82(2H, d, J=8.4Hz), 7.94(1H, d, J=1.4Hz)
22	p-methoxyphenyl		51	0.76~2.20(13H, m), 2.44(3H, s), 2.72(1H, dd, J=8.6.15Hz), 2.93(1H, dd, J=9.6.17.6Hz), 3.94(1H, dd, J=3.6.15Hz), 3.17(1H, dd, J=2.4.17.6Hz), 3.67(1H, dd, J=4, 8.6Hz), 3.88(3H, s), 4.02(1H, m), 4.23(1H, m), 6.93(2H, d, J=9Hz), 7.27(1H, s), 7.36(2H, d, J=8.2Hz), 7.52(1H, d, J=9.6Hz), 7.81(1H, d, J=8.4Hz), 7.91(2H, d, J=9Hz), 7.92(1H, d, J=1.8Hz)

Table 8 (continued)

Compd. of Ex. No.	R^1	R^2	[11] Yield%	[11] NMR(δ)
23	phenyl		70	0.7~2.05(13H, m), 2.96(1H, dd, J=18, 9.4Hz), 3.15(1H, dd, J=14.2, 7.8Hz), 3.21(1H, dd, J=18, 2.6Hz), 3.36(1H, dd, J=14.2, 4.2Hz), 3.80(1H, dd, J=7.8, 4.4Hz), 4.04(1H, m), 4.24(1H, m), 7.11(1H, d, J=1.6Hz), 7.41~7.63(3H, m), 7.94(2H, m), 8.75(1H, d, J=1.8Hz) (mp. 106~107℃)
24	4-pyridyl		70	0.70~1.85(13H, m), 2.04(3H, m), 3.02(1H, dd, J=18, 8.6Hz), 3.10~3.26(2H, m), 3.36(1H, dd, J=14.4, 4.2Hz), 3.82(1H, dd, J=7.6, 4.4Hz), 4.02(1H, m), 4.26(1H, m), 7.13(1H, d, J=1.6Hz), 7.59(1H, d, J=10Hz), 7.71(2H, dd, J=4.6, 1.6Hz), 8.76(1H, d, J=2Hz), 8.82(2H, dd, J=4.6, 1.6Hz) (mp. 118~120℃)
25	3-thienyl		72	0.70~1.87(13H, m), 2.28(3H, bs), 2.89(1H, dd, J=17.6, 9.4Hz), 3.10(1H, dd, J=17.6, 2.7Hz), 3.14(1H, dd, J=14.3, 7.8Hz), 3.35(1H, dd, J=14.3, 4.1Hz), 3.78(1H, dd, J=7.8, 4.3Hz), 4.00(1H, m), 4.20(1H, m), 7.12(1H, d, J=2.0Hz), 7.31(1H, dd, J=5.1, 2.9Hz), 7.52(1H, dd, J=5.1, 1.2Hz), 7.57(1H, s), 8.08(1H, dd, J=2.9, 1.2Hz), 8.75(1H, dd, J=2Hz)
26	cyclohexyl		69 Mp. 90-93	0.70~1.90(24H, m), 1.98(3H, bs), 2.32(1H, m), 2.45(1H, dd, J=9.8, 1.8Hz), 2.66(1H, dd, J=18, 2.8Hz), 3.15(1H, dd, J=14, 7.4Hz), 3.35(1H, dd, J=14.4, 3.8Hz), 3.80(1H, dd, J=7.4, 4.2Hz), 3.91(1H, m), 4.02(1H, m), 7.13(1H, d, J=1.6Hz), 7.50(1H, d, J=9.8Hz), 8.78(1H, d, J=1.8Hz)

Table 8 (continued)

Compd. of Ex. No.	R¹	R²	[II] Yield%	[II] [α]D° (C=1, CHCl3) (Temp. ℃)	[II] NMR(δ)
27	m-2-(N-morpholino)-ethoxyphenyl		76	-46.8 (23.5)	0.70~2.10(13H, m), 2.59(4H, t, J=4.7Hz), 2.82(2H, t, J=5.7Hz), 2.94(1H, dd, J=9.5, 17.9Hz), 3.15(1H, dd, J=7.6, 14.6Hz), 3.18(1H, dd, J=2.5, 17.9Hz), 3.34(1H, dd, J=4.1, 14.6Hz), 3.74(4H, t, J=9.3Hz), 3.74(1H, m), 4.02(1H, m), 4.15(2H, t, J=8.7Hz), 4.22(1H, m), 7.11(1H, br. s), 7.15(1H, d, J=2.7), 7.36(1H, t, J=8.2), 7.45~7.62(2H, m), 8.75(1H, d, J=1.1Hz)
28	m-(N-formyl)-methylamino-phenyl		73		0.77~1.85(13H, m), 2.40(2H, m), 3.02(1H, dd, J=9.0, 17.9Hz), 3.17(3H, m), 3.34(3H, s), 3.35(1H, m), 3.60(1H, dd, J=4.3, 7.8Hz), 4.03(1H, m), 4.25(1H, dt, J=2.1, 8.2Hz), 7.13(1H, d, J=2.0Hz), 7.38(1H, ddofd, J=8.0, 1.2, 2.3Hz), 7.52(1H, t, J=7.52Hz), 7.59(1H, d, J=9.7Hz), 7.79(2H, m), 8.52(1H, s), 8.75(1H, d, J=2.0)
29	N-methyl-3-pyrrolyl		69	-57.6 (24)	0.70~2.00(13H, m), 2.65(1H, dd, J=9.8, 16.8Hz), 2.94(1H, dd, J=2.4, 17Hz), 3.13(1H, dd, J=7.6, 14.4Hz), 3.35(1H, dd, J=4.2, 14.6Hz), 3.69(3H, s), 3.77(1H, dd, J=4.2, 8Hz), 3.99(1H, m), 4.13(1H, dt, J=9.6, 2Hz), 6.56(1H, s), 6.57(1H, s), 7.11(1H, d, J=1.8Hz), 7.27(1H, s), 7.53(1H, d, J=9.6Hz), 8.76(1H, d, J=2Hz)
30	N-morpholino-methyl		52		
31	N-pyperidino-methyl		36		
32	4-pyridyl		76		0.76~1.90(13H, m), 2.35(3H, bs), 2.67(3H, s), 3.14(4H, m), 3.80(1H, dd, J=4.2, 7.8Hz), 4.03(1H, m), 4.25(1H, m), 6.88(1H, s), 7.58(1H, d, J=9.6Hz), 7.71(2H, m), 8.81(2H, m)
33	phenyl		70		0.78~1.75(13H, m), 3.11(4H, m), 4.07(2H, m), 4.23(1H, m), 6.70(1H, s), 7.41(2H, dd, J=7.8, 15.3Hz), 7.57(1H, t, J=7Hz), 7.88(2H, d, J=7.2Hz), 8.49(1H, s)

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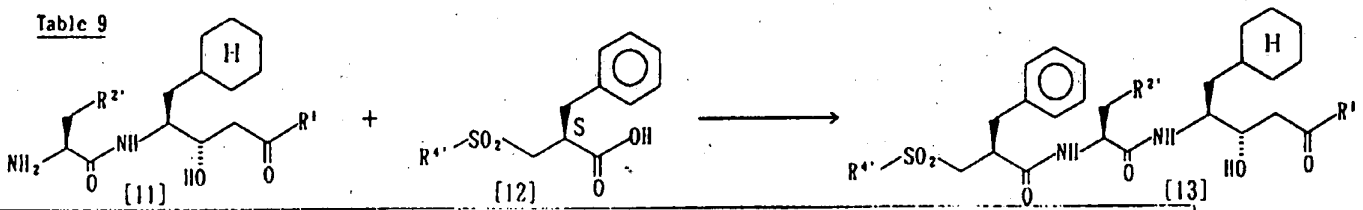
Table 8 (continued)

Compd. of Ex. No.	R^1	R^2	[II]		
			Yield%	$[\alpha]_D^{\circ}$ (C=1, $CHCl_3$) (Temp. ℃)	NMR(δ)
34	4-pyridyl	$-CONH_2$	17		
35	4-pyridyl	-SMe	88		0.70~1.80(13H, m), 2.13(3H, s), 2.73(1H, dd, J=8.2, 13.8Hz), 3.02(1H, dd, J=4, 13.6Hz), 3.09(1H, dd, J=8.6, 15.2Hz), 3.20(1H, dd, J=3.6, 18.4Hz), 3.58(1H, dd, J=4, 8.4Hz), 4.06(1H, m), 4.28(1H, m), 7.58(1H, d, J=10Hz), 7.72(2H, m), 8.81(2H, m)

Table 9



[11] + [12] → [13]

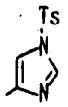
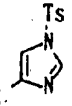
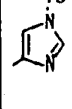
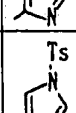
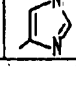
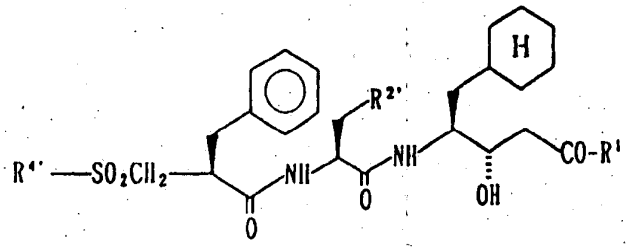
Compd. of Ex. No.	R¹	R⁴'	R²'	[13] Yield %	[13] IR ν max(cm⁻¹) or NMR(δ)
2	phenyl	tert-butyl		86	0.70~1.82(13H, m), 1.32(9H, s), 1.93(1H, bs), 2.44(3H, s), 2.75~3.14(7H, m), 3.21(1H, m), 3.48(1H, dd, J=13.9Hz), 3.98(1H, m), 4.20(1H, m), 4.56(1H, ddd, J=6.6, 6.6Hz), 6.44(1H, d, J=9.4Hz), 7.13~7.30(6H, m), 7.40~7.63(3H, m), 7.34(2H, d, J=8.4Hz), 7.80(2H, d, J=8.4Hz), 7.89(1H, d, J=1.2Hz), 7.96(2H, d, J=7.8Hz)
3	o-fluorophenyl	tert-butyl		73	0.70~1.80(13H, m), 1.34(9H, s), 2.15(2H, bs), 2.70~3.15(7H, m), 3.19(1H, m), 3.51(1H, dd, J=9.6, 13.4Hz), 3.97(1H, m), 4.15(1H, m), 4.58(1H, ddd, J=6.2, 6.2, 6.2Hz), 6.43(1H, d, J=9.0Hz), 7.18(1H, s), 7.05~7.41(7H, m), 7.34(2H, d, J=8.2Hz), 7.54(1H, m), 7.82(2H, d, J=8.6Hz), 7.87(1H, ddd, J=7.7, 1.9Hz), 7.96(1H, d, J=1.7Hz)
4	m-methoxyphenyl	tert-butyl		93	0.70~1.82(13H, m), 1.33(9H, s), 2.43(3H, s), 2.77~3.13(7H, m), 3.20(1H, m), 3.49(1H, dd, J=9, 16Hz), 3.86(3H, s), 3.48(1H, m), 4.18(1H, m), 4.56(1H, ddd, J=7, 7, 7Hz), 6.40(1H, d, J=9.0Hz), 7.21(1H, s), 7.09~7.40(7H, m), 7.52(2H, m), 7.80(2H, d, J=8.4Hz), 7.87(1H, d, J=1.4Hz)
5	p-methylphenyl	tert-butyl		79	3400, 3260, 3140, 1665, 1625, 1605, 1498, 1450, 1370, 1172, 1115, 1030, 1010
6	2,4-difluoro-phenyl	tert-butyl		76	3400(br), 1665, 1600, 1599(sh), 1500, 1475, 1175, 970, 855
7	1-naphthyl	tert-butyl		41	3696, 3416, 1667, 1598, 1509, 1477, 1450, 1385, 1292, 1175, 1117, 1094, 1080

Table 9 (continued)



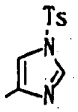
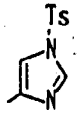
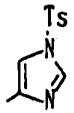
Compd. of Ex. No.	R¹	R⁴'	R²'	[13] Yield %	[13] IR νmax(cm⁻¹) or NMR(δ)
8	3-thienyl	tert-butyl		74	3410. 3360(sh). 1665. 1598. 1510. 1385. 1173. 1116. 1093. 1078
9	2-thiazolyl	tert-butyl		81	0. 7~1. 82(13H, m). 1. 35(9H, s). 2. 37(1H, bs). 2. 43(3H, s). 2. 78~3. 28(8H, m). 3. 53(1H, dd, J=9. 0, 13. 0Hz). 3. 97(1H, m). 4. 18(1H, m). 4. 58(1H, ddd, 6. 4, 6. 4, 6. 4Hz). 6. 35(1H, d, J=9. 0Hz). 7. 05(1H, d, J=6. 4Hz). 7. 20(1H, s). 7. 13~7. 40(5H, m). 7. 33(2H, d, J=8. 4Hz). 7. 68(1H, d, J=3. 2Hz). 7. 80(2H, d, J=8. 4Hz). 8. 00(1H, d, J=1. 2Hz). 8. 01(2H, d, J=3Hz)
10	m-fluorophenyl	tert-butyl		83	3460. 3360. 3280. 3160. 1665. 1625. 1590. 1500. 1450. 1115. 1032. 1010

Table 9 (continued)

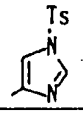
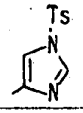
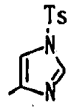
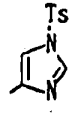
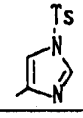
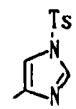
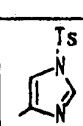
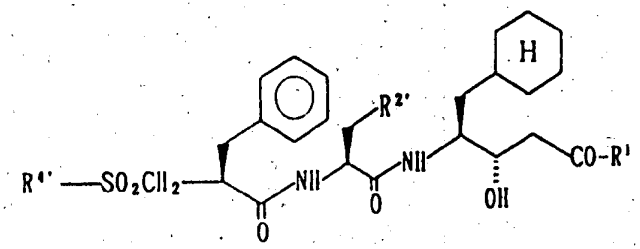
Compd. of Ex. No.	R^1	$R^{4'}$	$R^{2'}$	Yield %	[13] IR or NMR
11	p-fluorophenyl	tert-butyl		71	3410, 3280, 3160, 1665, 1625, 1600, 1509, 1450, 1155, 1115, 1030, 1010
12	2,6-difluoro-phenyl	tert-butyl		97	3420, 1660, 1624, 1599, 1499, 1467, 1459, 1385, 1292, 1189, 1175, 1118, 1093, 1085, 1018
13	o-methoxyphenyl	tert-butyl		79	0.70~1.80(13H, m), 1.33(9H, s), 2.42(3H, s), 2.78~3.25(7H, m), 3.50(1H, dd, J=18.13Hz), 3.88(3H, s), 3.95(1H, m), 4.10(1H, m), 4.48(1H, ddd, J=6.5, 6.5, 6.5Hz), 6.48(1H, d, J=9Hz), 6.97(2H, m), 7.06~7.40(9H, m), 7.49(1H, m), 7.73(1H, dd, J=9.2Hz), 7.79(2H, d, J=8Hz), 7.84(1H, s)
14	o-chlorophenyl	tert-butyl		81	0.70~1.80(13H, m), 1.31(9H, s), 2.40(3H, s), 2.80~3.22(7H, m), 3.50(1H, dd, J=15.7.5Hz), 3.93(1H, m), 4.09(1H, m), 4.51(1H, ddd, J=6.4, 6.4, 6.4Hz), 6.29(1H, d, J=10Hz), 7.03~7.41(8H, m), 7.53(1H, m), 7.78(2H, d, J=8.4Hz), 7.78(1H, d, J=1.4Hz)
15	m-cyanophenyl	tert-butyl		84	3408, 2236, 1668, 1599, 1508, 1478, 1450, 1368, 1291, 1190, 1175, 1117, 1079, 908
16	o-methyl-sulfonyl-aminophenyl	tert-butyl			3420, 1666, 1607, 1578, 1499, 1452, 1387, 1340, 1290, 1174, 1155, 1117, 1079, 968, 909
17	p-trifluoromethyl phenyl	tert-butyl		85	3400~3200, 3140, 1665, 1625, 1600, 1510, 1450, 1410, 1325, 1175, 1135, 1115 1065

Table 9 (continued)



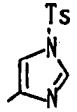
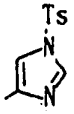
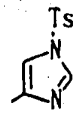
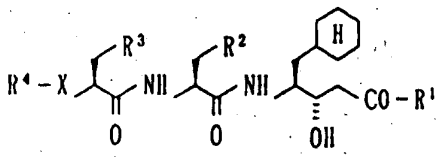
Compd. of Ex. No.	R¹	R⁴'	R²'	[13] Yield %	[13] NMR(δ)
18	m-morpholino-carbonyloxyphenyl	tert-butyl		79	0.70~1.82(13H, m), 1.90(1H, bs), 1.32(9H, s), 2.43(3H, s), 2.74~3.30(7H, m), 3.49(1H, dd, J=14.10Hz), 3.52~3.82(8H, m), 3.96(1H, m), 4.16(1H, m), 4.54(1H, ddd, J=6.2, 6.2, 6.2Hz), 6.40(1H, d, J=9.4Hz), 7.10~7.40(7H, m), 7.33(2H, d, J=8.2Hz), 7.48(1H, t, J=7.5Hz), 7.70(1H, m), 7.80(2H, d, J=8.4Hz), 7.80(1H, m), 7.89(1H, d, J=1.2Hz)
19	m-morpholino-carbonylphenyl	tert-butyl		85	0.7~1.82(13H, m), 1.32(9H, s), 2.43(3H, s), 2.70~3.30(8H, m), 3.48(1H, dd, J=9.4, 12.8Hz), 3.30~3.90(8H, m), 3.99(1H, m), 4.20(1H, m), 4.53(1H, ddd, J=6.2, 6.2, 6.2Hz), 6.42(1H, d, J=9.4Hz), 7.08~7.31(6H, m), 7.34(2H, d, J=8.2Hz), 7.45~7.68(2H, m), 7.81(2H, d, J=8.4Hz), 7.91(1H, d, J=1.4Hz), 8.05(2H, m)
20	3',4'-methylene-dioxyphenyl	tert-butyl		89	0.7~1.8(13H, m), 1.9(1H, bs), 1.33(9H, s), 2.44(3H, s), 2.74~3.30(7H, m), 3.50(1H, dd, J=9.2, 13Hz), 3.96(1H, m), 4.16(1H, m), 4.56(1H, ddd, J=6.4, 6.4, 6.4Hz), 6.06(2H, s), 6.40(1H, d, J=9.2Hz), 6.85(1H, d, J=8.2Hz), 7.25(6H, m), 7.34(1H, d, J=8.2Hz), 7.45(1H, d, J=1.6Hz), 7.56(1H, dd, J=8.2, 1.6Hz), 7.80(2H, d, J=8.4Hz), 7.85(1H, d, J=1.4Hz)

Table 9 (continued)

Compd. of Ex. No.	R¹	R⁴'	R²'	Yield %	[13] NMR(δ)
21	cyclohexyl	tert-butyl		86	0.70~1.90(23H, m), 1.34(9H, s), 2.33(1H, m), 2.44(3H, s). 2.78~3.27(8H, m), 3.50(1H, dd, J=12.0, 8.4Hz), 3.86(1H, m), 3.96(1H, m). 4.54(1H, ddd, J=6.2, 6.2, 6.2Hz), 6.35(1H, d, J=10Hz), 7.13~7.34(6H, m). 7.37(2H, d, J=8.4Hz), 7.82(2H, d, J=8.4Hz), 7.90(1H, d, J=1.4Hz).
22	p-methoxyphenyl	tert-butyl		87	0.72~1.80(13H, m), 0.90(1H, bs), 1.33(9H, s), 2.43(3H, s). 2.78~3.12(7H, m), 3.20(1H, m), 3.49(1H, dd, J=9.4, 13.2Hz), 3.88(3H, s). 3.97(1H, dd, J=9.4, 13.2Hz), 3.88(3H, s), 3.97(1H, ddd, J=7.4, 7.4, 7.4Hz). 4.17(1H, m), 4.57(1H, ddd, J=6.6, 6.6Hz), 6.42(1H, d, J=9.4Hz). 6.94(2H, d, J=9Hz), 7.16~7.26(6H, m), 7.22(1H, s), 7.34(2H, d, J=8Hz). 7.79(2H, d, J=8.4Hz), 7.84(1H, d, J=1.2Hz), 7.94(2H, d, J=9Hz)

Table 9 (continued)



Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[13] ([IA]) Yield%	NMR(δ)
23	phenyl			CH_2	$+SO_2$	86	0.7~1.88(13H, m), 1.32(9H, s), 2.83~3.55(9H, m), 3.96(1H, m), 4.15(1H, m), 4.74(1H, ddd, J=5.6Hzx3), 6.32(1H, d, J=9.8Hz), 7.13(1H, d, J=2Hz), 7.25(5H, m), 7.47(2H, t, J=7.8Hz), 7.57(1H, d, J=7.8Hz), 7.96(2H, d, J=7.2Hz), 8.65(1H, d, J=2Hz)
24	4-pyridyl			CH_2	$+SO_2$	86	0.60~1.80(13H, m), 1.33(9H, s), 1.88(2H, bs), 2.86~3.50(9H, m), 3.99(1H, m), 4.15(1H, m), 4.66(1H, ddd, J=6Hzx3), 6.33(1H, d, J=9.2Hz), 7.16(1H, d, J=0.6Hz), 7.28(5H, m), 7.65(1H, d, J=6Hz), 7.82(2H, bs), 8.69(1H, d, J=0.6Hz), 8.82(2H, bs)
25	3-thienyl			CH_2	$+SO_2$	79	0.65~1.82(13H, m), 1.33(9H, s), 2.82~3.55(9H, m), 3.95(1H, m), 4.15(1H, m), 4.72(1H, ddd, J=6Hzx3), 6.33(1H, d, J=9.4Hz), 7.14(1H, d, J=2Hz), 7.17~7.38(6H, m), 7.55(1H, dd, J=5.2, 1.4Hz), 7.55(1H, s), 8.20(1H, dd, J=1.2, 2.8Hz), 8.67(1H, d, J=2Hz)
26	cyclohexyl			CH_2	$+SO_2$	87	0.7~2.00(24H, m), 1.35(9H, s), 2.32(1H, m), 2.88~3.58(9H, m), 3.83(1H, m), 3.92(1H, m), 4.70(1H, ddd, J=5.2Hzx3), 6.30(1H, d, J=9.8Hz), 7.16(1H, d, J=2Hz), 7.27(5H, m), 7.50(1H, d, J=5.8Hz), 8.71(1H, d, J=2.2Hz)
27	m-2-(N-morpholino)ethoxy-phenyl			CH_2	$+SO_2$	91	0.6~1.8(13H, m), 2.60(4H, m), 2.84(2H, t, J=11.2Hz), 2.89~3.62(9H, m), 3.75(4H, m), 3.95(1H, ddd, J=7.8Hzx3), 4.18(2H, t, J=5.4Hz), 4.18(1H, m), 4.73(1H, ddd, J=5.2Hzx3), 6.32(1H, d, J=9.4Hz), 7.14(1H, d, J=2Hz), 7.14(1H, m), 7.22~7.56(3H, m), 8.67(1H, d, J=2Hz)

Table 9 (continued)

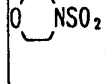
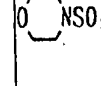
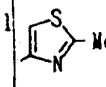
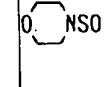
Compd. of Ex. No.	R¹	R²	R³	X	R⁴	[13] ([IA]) Yield%	NMR(δ)
28	m-(N-formyl)methylaminophenyl			NH		91	0.60~1.78(13H, m), 2.51(2H, m), 2.84(4H, m), 3.17(2H, m), 3.37(3H, s), 3.40(5H, m), 3.54(1H, dd, J=4.1, 10Hz), 3.96(2H, m), 4.14(1H, m), 4.74(1H, m), 5.20(1H, d, J=5.7Hz), 6.60(1H, d, J=6.6Hz), 7.15(1H, d, J=1.9Hz), 7.34(5H, m), 7.53(1H, t, J=8.9Hz), 7.89(2H, m), 8.61(1H, s), 8.84(1H, d, J=2.1Hz), 9.26(1H, d, J=7.2Hz)
29	N-methylpyrrolyl			CH_2		85	0.70~1.80(13H, m), 2.63(1H, dd, J=9.6, 16.8Hz), 2.80(1H, dd, J=2.5, 16.8Hz), 2.95(2H, m), 3.07~3.33(3H, m), 3.48(2H, m), 3.69(3H, s), 3.90(1H, ddd, J=7.4Hzx3), 4.06(1H, m), 4.75(1H, ddd, J=5.6Hz), 6.36(1H, d, J=9.6Hz), 6.57(1H, s), 6.58(1H, s), 7.11(1H, d, J=1.8Hz), 7.28(6H, m), 7.49(1H, d, J=6.8Hz), 8.69(1H, d, J=2Hz)
30	(N-morpholino)-methyl			NH		48	0.58~2.00(13H, m), 2.58(8H, m), 2.98(3H, m), 3.27(4H, m), 3.60(1H, dd, J=4.8, 14.8Hz), 3.80(6H, m), 4.15(2H, m), 4.78(1H, m), 5.03(1H, d, J=4.5Hz), 6.60(1H, d, J=9.4Hz), 7.18(1H, d, J=1.8Hz), 7.44(1H, s), 7.45(1H, ddd, J=7Hzx3), 7.61(1H, t, J=7.2Hz), 7.72(1H, t, J=7.0Hz), 7.86(1H, d, J=8.2Hz), 7.94(1H, d, J=7.0Hz), 8.42(1H, d, J=8.2Hz), 8.86(1H, d, J=1.8Hz), 9.45(1H, d, J=7.8Hz)
31	(N-pyperidino)-methyl			NH		58	0.60~2.08(19H, m), 2.54(7H, m), 2.71(2H, m), 2.99(3H, m), 3.22(1H, m), 3.28(2H, s), 3.60(1H, dd, J=5.15Hz), 3.80(2H, m), 4.14(2H, m), 4.80(1H, m), 5.07(1H, bs), 6.64(1H, d, J=8.6Hz), 7.18(1H, d, J=1.8Hz), 7.45(2H, ddd, J=7.0Hzx3), 7.60(1H, t, J=6.6Hz), 7.70(1H, t, J=6.6Hz), 7.86(1H, d, J=8.6Hz), 7.94(1H, d, J=7.8Hz), 8.24(1H, d, J=8.6Hz), 8.84(1H, d, J=1.8Hz), 9.34(1H, d, J=7.4Hz)
32	4-pyridyl			NH		95	0.78~1.68(13H, m), 2.45(2H, m), 2.75(3H, s), 2.83(3H, m), 3.10(3H, m), 3.43(4H, m), 3.45(2H, m), 3.97(2H, m), 4.12(1H, m), 4.75(1H, m), 5.16(1H, d, J=5Hz), 6.70(1H, d, J=9.4Hz), 6.92(1H, s), 7.33(5H, m), 7.82(2H, bs), 8.85(2H, bs), 9.22(1H, d, J=7.6Hz)

Table 9 (continued)

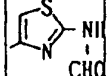
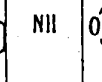
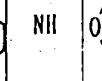
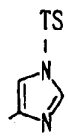
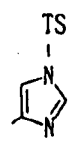
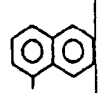
Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[13] ([IA]) Yield%	NMR(δ)
33	phenyl			CH_2	$+SO_2$	71	0.70~1.85(13H, m), 1.30(9H, s), 2.84(1H, m), 3.14(7H, m), 3.46(1H, m), 4.06(1H, m), 4.13(1H, ddd, J=7Hz), 4.63(1H, m), 6.40(1H, d, J=10Hz), 6.79(1H, s), 7.25(5H, m), 7.48(2H, t, J=7.5Hz), 7.57(1H, m), 7.97(2H, m), 8.51(1H, m)
34	4-pyridyl	$-CONH_2$		NH		70	0.79~1.78(13H, m), 2.10(2H, m), 2.50(2H, m), 2.68(3H, m), 2.96(4H, m), 3.13(2H, m), 3.93(1H, dd, J=3.6, 14.2Hz), 4.05(1H, m), 4.21(2H, m), 4.78(1H, m), 7.28(1H, d, J=9.0Hz), 7.44(2H, d, J=4.4Hz), 7.58(2H, m), 7.88(4H, m), 8.20(1H, d, J=7.8Hz), 8.50(1H, d, J=8.0Hz), 8.80(2H, bs)
35	4-pyridyl	-SMe		NH		84	0.80~1.80(13H, m), 2.14(3H, s), 2.63(2H, m), 2.96(1H, m), 3.26(3H, m), 3.49(4H, m), 3.98(1H, dddd, J=5.0Hzx4), 4.12(1H, m), 4.25(1H, m), 4.65(1H, ddd, J=5.8Hz), 4.99(1H, d, J=5.4Hz), 6.90(1H, d, J=10Hz), 7.30(5H, m), 7.78(2H, bs), 8.83(2H, bs)
36	4-pyridyl			CH_2	$+SO_2$	89	0.78~1.80(13H, m), 2.95~3.55(10H, m), 3.99(1H, ddd, J=7.8Hz), 4.18(1H, m), 4.63(1H, ddd, J=5.6Hz), 6.39(1H, d, J=9.4Hz), 7.11(1H, d, J=1.8Hz), 7.38(2H, d, J=5.2Hz), 7.58(3H, m), 7.76(3H, m), 7.89(1H, m), 8.03(1H, d, J=7.8Hz), 8.54(1H, d, J=1.8Hz), 8.80(2H, bs)
37	phenyl			CH_2		89	0.70~1.82(13H, m), 1.22(3H, d, J=7Hz), 1.30(3H, d, J=7Hz), 1.90(1H, bs), 2.43(3H, s), 2.72~3.23(8H, m), 3.49(1H, dd, J=13.2, 9.6Hz), 3.99(1H, m), 4.19(1H, m), 4.57(1H, ddd, J=6Hzx3), 6.40(1H, d, J=9.4Hz), 7.96(2H, d, J=6.8Hz), 7.15~7.32(6H, m), 7.34(2H, d, J=8.4Hz), 7.42~7.63(3H, m), 7.85(2H, d, J=8.4Hz), 7.85(1H, d, J=8.4Hz)
38	phenyl			CH_2		98	0.70~1.83(13H, m), 1.23(3H, t, J=7.4Hz), 2.43(3H, s), 2.20(2H, bs), 2.65~3.24 (8H, m), 3.50(1H, dd, J=9.6, 14.2Hz), 4.00(1H, m), 4.19(1H, m), 4.57(1H, ddd, J=6.2Hzx3), 6.43(1H, d, J=9.4Hz), 7.06~7.40(8H, m), 7.40~7.63(3H, m), 7.80(2H, d, J=8.4Hz), 7.88(1H, s), 7.97(2H, d, J=1.8Hz)

Table 9 (continued)

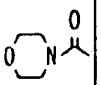
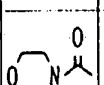
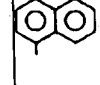
Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[13] ([IA]) Yield%	NMR(δ)
39	phenyl			CH_2		76	0.70~1.80(13H, m), 2.28(1H, dd, J=6.2, 16.4Hz), 2.66(1H, dd, J=4, 16.8Hz), 2.92(3H, m), 3.05~3.75(12H, m), 4.06(1H, m), 4.19(1H, m), 4.79(1H, ddd, J=6.2Hz), 6.78(1H, d, J=10Hz), 7.18(1H, d, J=1.8Hz), 7.30~7.57(7H, m), 7.77(1H, d, J=7.8Hz), 7.88(1H, m), 8.04(3H, m), 8.29(1H, d, J=6.4Hz), 8.69(1H, d, J=1.8Hz)
40	phenyl			CH_2		81	0.80~1.80(13H, m), 2.40(3H, s), 2.90~3.75(17H, m), 4.06(1H, m), 4.22(1H, d, J=9.2Hz), 4.63(1H, ddd, J=5Hz), 6.87(1H, d, J=9.6Hz), 7.18~7.59(9H, m), 7.74~8.14(10H, m)
41	4-pyridyl			CH_2		76	0.70~1.79(13H, m), 2.25(1H, dd, J=6.6, 17Hz), 2.74(1H, dd, J=3.8, 16.8Hz), 2.88(1H, dd, J=3.6, 16Hz), 2.96(3H, m), 3.08~3.64(10H, m)3.75(1H, dd, J=4.8, 13Hz), 4.12(2H, m), 4.75(1H, ddd, J=5.8Hzx3), 6.82(1H, d, J=9.4Hz), 7.19(1H, d, J=2Hz), 8.77(2H, bs), 7.28(1H, d, J=7.6Hz), 7.41(1H, t, J=7Hz), 7.54(2H, m), 7.78(1H, d, J=8Hz), 7.87(3H, m), 8.03(1H, m), 8.46(1H, d, J=6.2Hz), 8.71(1H, d, J=2Hz)
42	4-pyridyl			CH_2		79	
43	4-pyridyl			NH		95	0.70~1.90(13H, m), 2.49(2H, m), 2.87(3H, m), 3.15(3H, m), 3.41(4H, m), 3.57(2H, m), 3.97(2H, m), 4.11(1H, m), 4.74(1H, m), 5.11(1H, d, J=5Hz), 6.59(1H, d, J=9.2Hz), 7.15(1H, d, J=2Hz), 7.32(5H, m), 7.85(2H, m), 8.85(1H, d, J=2Hz), 8.85(2H, m), 9.34(1H, d, J=7Hz)
44	4-pyridyl			NH		96	0.76~1.86(13H, m), 1.95(2H, m), 2.50(2H, m), 2.66(2H, m), 2.88~3.29(6H, m), 3.58(1H, dd, J=5, 15Hz), 3.98(1H, m), 4.13(3H, m), 4.79(1H, m), 5.05(1H, d, J=4.5Hz), 6.63(1H, d, J=10Hz), 7.17(1H, d, J=1.7Hz), 7.43(2H, m), 7.59(2H, m), 7.88(4H, m), 8.69(1H, m), 8.85(1H, d, J=2Hz), 8.55(2H, bs), 9.51(1H, d, J=7Hz)

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Table 9 (continued)

Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[13] ([IA]) Yield%	NMR(δ)
45	cyclohexyl			NH		94	0.77~1.85(23H, m), 2.36(1H, m), 2.56(4H, m), 2.85(3H, m), 3.18(1H, dd, J=5.2, 14.4Hz), 3.49(6H, m), 3.90(3H, m), 4.75(1H, m), 5.01(1H, d, J=5.8Hz), 6.55(1H, d, J=9.2Hz), 7.16(1H, d, J=1.8Hz), 7.32(5H, m), 8.84(1H, d, J=1.8Hz), 9.10(1H, d, J=7.2Hz)
46	4-pyridyl			NH		89	0.77~1.80(13H, m), 2.35(6H, s), 2.75(1H, dd, J=10.6, 13.8Hz), 3.15(3H, m), 3.43(1H, dd, J=3.8, 13.8Hz), 3.55(1H, dd, J=4.2, 15Hz), 3.75(1H, m), 3.95(2H, m), 4.12(1H, m), 4.73(1H, m), 4.98(1H, d, J=5Hz), 6.63(1H, d, J=9.4Hz), 7.13(1H, d, J=2Hz), 7.31(5H, m), 7.85(2H, bs), 8.84(1H, d, J=2), 8.84(2H, bs), 9.39(1H, d, J=7.2Hz)
47	4-pyridyl			NH		90	0.79~1.80(13H, m), 2.30(2H, m), 2.42(2H, m), 2.85~3.62(11H, m), 3.94(1H, m), 4.00(1H, m), 4.20(1H, m), 4.42(1H, m), 4.75(1H, m), 6.63(1H, d, J=9.4Hz), 7.16(1H, d, J=2Hz), 7.29(5H, m), 7.71(1H, d, J=4.4Hz), 7.85(2H, m), 8.33(1H, d, J=7Hz), 8.62(1H, d, J=2Hz), 8.83(2H, bs)
48	4-pyridyl			NH		94	0.79~1.76(13H, m), 2.20(2H, m), 2.49(2H, m), 2.80~3.08(4H, m), 3.19~3.56(7H, m), 3.92(1H, dd, J=4.4, 14.2Hz), 4.00(1H, m), 4.20(1H, m), 4.55(1H, m), 4.74(1H, m), 6.65(1H, d, J=9.6Hz), 7.15(1H, d, J=1.6Hz), 7.45(2H, d, J=5.4Hz), 7.57(2H, m), 7.85(4H, m), 8.19(1H, m), 8.33(1H, d, J=7), 8.52(1H, d, J=2Hz), 8.83(2H, bs)
49	m-2-(N-morpholino)ethoxyphenyl			NH		77	0.82~1.80(13H, m), 2.19(2H, m), 2.33(2H, m), 2.60(4H, m), 2.77~3.25(6H, m), 3.43(7H, m), 3.74(4H, m)3.83(1H, dd, J=5, 15Hz), 3.98(1H, m), 4.21(3H, m), 4.63(1H, m), 4.76(1H, dddd, J=5.2Hzx4), 4.76(1H, m), 6.64(1H, d, J=9.8Hz), 7.12(1H, d, J=1.4Hz), 7.15(1H, m), 7.41(3H, m), 7.55(3H, m), 7.67(2H, m), 7.84(2H, m), 8.17(1H, m), 8.54(1H, d, J=2Hz)
50	4-pyridyl			NH		83	0.60~1.80(13H, m), 3.08(5H, m), 3.33(4H, m), 3.57(2H, m), 3.64(4H, m), 4.05(1H, m), 4.18(1H, m), 4.65(1H, m), 4.95(1H, bs), 6.87(1H, d, J=9.8Hz), 7.17(1H, d, J=1.2Hz), 7.30(5H, m), 8.17(2H, m), 8.58(1H, d, J=9Hz), 8.70(1H, d, J=1.2Hz), 8.84(2H, m)

Table 9 (continued)

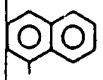
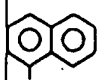
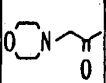
Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[13] ([IA]) Yield%	NMR(δ)
51	m-2-(N-morpholino)ethoxyphenyl			CH_2		70	0.70~1.80(13H, m), 2.28(1H, dd, J=6.6, 17.5Hz), 2.56(4H, m), 2.68(1H, dd, J=4.16.6Hz), 2.80(3H, m), 2.95(1H, m), 3.18(2H, m), 3.35(4H, m), 3.50(2H, m), 3.63(1H, dd, J=5.4.12Hz), 3.71(4H, t, J=4.4Hz), 3.87(1H, d, J=7.4Hz), 4.05(1H, m), 4.16(3H, t, J=5.6Hz), 4.77(1H, ddd, J=6.4Hzx3), 6.79(1H, d, J=9.6Hz), 7.09(1H, dd, J=2.4.8Hz), 7.18(1H, d, J=1.8Hz), 7.35(3H, m), 7.54(3H, m), 7.63(1H, d, J=7.8Hz), 7.77(1H, d, J=7.6Hz), 7.88(1H, m), 8.02(1H, m), 8.28(1H, d, J=6.4Hz), 8.70(1H, d, J=1.8Hz)
52	cyclohexyl			NH		94	0.78(23H, m), 2.22(2H, m), 2.38(2H, m), 2.58(2H, m), 3.00(3H, m), 3.48(6H, m), 3.82(1H, dd, J=5, 14.6Hz), 3.82(1H, m), 3.98(1H, m), 4.63(1H, m), 4.74(1H, ddd, J=8.8Hz), 6.56(1H, d, J=8.8Hz), 7.12(1H, d, J=1.8Hz), 7.44(2H, m), 7.58(2H, dt, J=1.8, 6.4Hz), 7.80(1H, m), 7.89(1H, m), 8.11(1H, d, J=7.8Hz), 8.22(1H, d, J=7.2Hz), 8.54(1H, d, J=1.8Hz)

Table 9 (continued)

Compd. of Ex. No.	$[\alpha]_D^{\circ}$ C=1.0, $CHCl_3$ (Temp. °C)	Molecular formula (Molecular weight)	Calcd.	Found	IR $\nu_{max}^{CHCl_3}$ cm^{-1}
23	-20.1 (24)	$C_{37}H_{40}N_3O_6S_2 \cdot {}^1/_2H_2O$ (704.94)	C:63.04 H:7.15 N:5.96 S:9.10	C:63.28 H:7.21 N:5.91 S:8.97	3520, 3420, 3360(br) 1670, 1600, 1580, 1450, 1118
24	-22.6 (24)	$C_{36}H_{48}N_4O_6S_2 \cdot {}^1/_4H_2O$ (708.93)	C:61.65 H:6.77 N:7.99 S:9.14	C:61.47 H:7.02 N:8.01 S:8.91	3410, 3360, 1665, 1605, 1505, 1505, 1450, 1410, 1115
25	-23.1 (25)	$C_{35}H_{47}N_3O_6S_3$ (701.948)	C:59.89 H:6.75 N:5.99 S:13.70	C:59.68 H:6.71 N:5.89 s:13.41	3315, 1665, 1510, 1412, 1290, 1115
26	-19.6 (24)	$C_{37}H_{55}N_3O_6S_2 \cdot {}^1/_2H_2O$ (710.99)	C:62.51 H:7.94 N:5.91 S:9.02	C:62.60 H:8.05 N:5.76 S:8.87	3520, 3420, 3360, (br-sh), 1665, 1605, 1510, 1450, 1118
27	-14.4 (23.5)	$C_{43}H_{60}N_4O_8S_2 \cdot {}^1/_2H_2O$ (834.101)	C:61.92 H:7.37 N:6.72 S:7.69	C:61.77 H:7.51 N:6.52 S:7.41	3500, 3420, 3360, 1665, 1596, 1581, 1505, 1460, 1448
28	(24.0) -23.2 (MeOH)	$C_{38}H_{50}N_6O_8S_2 \cdot {}^2/_3H_2O \cdot {}^1/_2CH_2Cl_2$ (836.462)	C:55.23 H:6.30 N:10.04 S:7.66	C:55.02 H:6.07 N:10.01 S:7.44	3370, 1672, 1603, 1586, 1511, 1450, 1406, 1341, 1262, 1158, 1116
29	-24.1 (24.0)	$C_{36}H_{50}N_4O_6S_2 \cdot {}^1/_2H_2O \cdot {}^1/_4iPr_2O$ (733.490)	C:61.41 H:7.49 N:7.64 S:8.74	C:61.28 H:7.43 N:7.50 S:8.50	3500, 3420, 3360, 1660, 1605, 1530, 1508, 1462, 1450
30		$C_{39}H_{54}N_6O_8S_2 \cdot {}^3/_2H_2O \cdot {}^3/_4iPr_2O$ (902.655)	C:57.88 H:7.54 N:9.31 S:7.10	C:57.65 H:7.31 N:9.59 S:6.88	3380(3300), 1712, 1665, 1600(1535), 1510, 1455, 1430

Table 9 (continued)

Compd. of Ex. No.	$[\alpha]_D^{\circ}$ C=1.0, $CHCl_3$ (Temp. ℃)	Molecular formula (Molecular weight)	Calcd.		Found		IR $\nu_{max}^{CHCl_3}$ cm^{-1}
31		$C_{40}H_{50}N_6O_7S_2 \cdot H_2O \cdot {}^1/_4iPr_2O$ (840.587)	C:59.30 N:10.00	H:7.37 S:7.63	C:59.44 N:9.88	H:7.45 S:7.55	3380(3280), 1705, 1662, 1600, 1535, 1510, 1450, 1400
32	-37.0 (24) 162-64	$C_{36}H_{48}N_6O_7S_2 \cdot {}^1/_4H_2O$ (745.044)	C:58.01 N:11.27	H:6.56 S:8.60	C:57.94 N:11.36	H:6.53 S:8.36	3560, 3380(3300), 1675, 1602, 1595, 1510(1535), 1455
34		$C_{37}H_{48}N_6O_8S \cdot {}^1/_2H_2O$ (745.876)	C:59.58 N:11.27	H:6.62 S:4.30	C:59.37 N:11.39	H:6.66 S:4.25	3600, 3360, 1732, 1685, 1664, 1640, 1600, 1545
35	-62.6 (24) 175-8	$C_{23}H_{47}N_5O_7S_2 \cdot {}^1/_2H_2O$ (698.886)	C:56.71 N:10.02	H:6.92 S:9.17	C:56.60 N:9.87	H:6.77 S:9.01	3600, 3380, 1670(1690), 1600, (1515, 1525) 1500
36	-14.5(24)	$C_{43}H_{60}N_4O_8S_2 \cdot {}^3/_2H_2O \cdot {}^1/_2iPr_2O$ (825.074)	C:62.60 N:6.79	H:7.33 S:7.77	C:62.65 N:6.79	H:7.13 S:7.59	3500, 3400, 3370, 1665, 1598, 1510, (sh, 1550, 1525)
39	98-100	$C_{42}H_{50}N_4O_6S \cdot {}^1/_2H_2O$ (749.952)	C:67.45 N:7.49	H:6.87 S:4.29	C:67.47 N:7.54	H:6.93 S:4.23	
41	-19.7 (25.5)	$C_{41}H_{49}N_5O_6S \cdot H_2O$ (757.947)	C:64.97 N:9.24	H:6.78 S:4.23	C:65.08 N:9.21	H:6.82 S:3.95	3400, 3340, 1665, (sh, 1695), 1625, 1530, 1510, 1450, 1410
43	-33.2 (25.5)	$C_{35}H_{46}N_6O_7S_2$ (726.921)	C:57.83 N:11.56	H:6.38 S:8.82	C:57.89 N:11.47	H:6.36 S:8.72	3560, 3540, 3380, (sh, 3300), 1665, 1500, 1530, 1510

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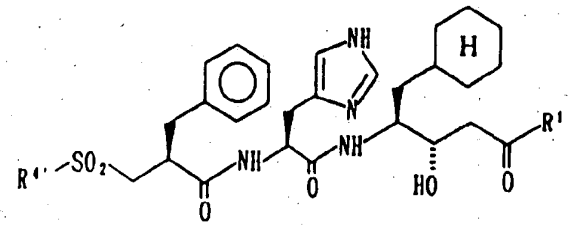
Table 9 (continued)

Compd. of Ex. No.	$[\alpha]_D^{25}$ C=1.0, $CHCl_3$ (Tcmp. °C)	Molecular formula (Molecular weight)	Calcd.	Found	IR $\nu_{max}^{CHCl_3}$ cm^{-1}
14	-40.7(24) 108-110	$C_{41}H_{53}N_2O_{15}S_2$ (830.014)	C:59.33 H:6.44 N:10.13 S:7.73	C:59.40 H:6.50 N:10.04 S:7.50	3560, 3520, 3390. (sh 3300), 1670, 1600, 1535 , 1510
15	-34.6 (24)	$C_{36}H_{53}N_5O_{17}S$ $\cdot^3/_4H_2O\cdot^1/_2iPr_2O$ (796.551)	C:58.80 H:7.78 N:8.79 S:8.05	C:58.55 H:7.55 N:9.05 S:7.77	3540, 3380, 3300, 1670, 1605, 1530, 1510, 1450, 1408
16	-32.0 (25)	$C_{33}H_{44}N_6O_6S_3$ $\cdot^1/_2H_2O\cdot^1/_2iPr_2O$ $\cdot^1/_4CHCl_2$ (766.200)	C:56.83 H:6.91 N:10.97 S:8.37	C:66.85 H:6.82 N:11.14 S:8.01	3550, 3380(3300), 1665 , 1605, 1596, 1530, 1510 , 1455, 1450
17		$C_{37}H_{48}N_6O_6S$ $\cdot^3/_2H_2O\cdot^1/_{10}iPr_2O$ (733.120)	C:60.71 H:7.03 N:11.46 S:4.37	C:60.79 H:7.05 N:11.56 S:4.31	
18	-23.0(25)	$C_{41}H_{50}N_6O_6S$ $\cdot^5/_4H_2O$ (777.444)	C:68.34 H:6.81 N:10.81 S:4.12	C:63.34 H:6.92 N:10.64 S:3.81	3520, 3340, 1670, 1600, 1510(1530)
19	-19.3(25)	$C_{48}H_{62}N_6O_8S$ $\cdot^3/_2H_2O$ (910.114)	C:63.34 H:7.20 N:9.23 S:3.52	C:63.49 H:7.27 N:9.35 S:3.36	3520, 3340, 1670, 1598, 1580, 1510, (sh 1530)
50	-21.8 (24)	$C_{36}H_{46}N_6O_6S_2$ $\cdot H_2O\cdot^1/_5\cdot D_2O$ (729.31)		C:61.35 H:7.03 N:11.36 S:4.16	3430(3480)3320, 1670, 1640, 1603, 1510

Table 9 (continued)

Compd. of Ex. No.	$[\alpha]_D^{25}$ (C=1.0, MeOH (Temp. °C)	Molecular formula (Molecular weight)	Calcd.	Found	IR $\nu_{max}^{CHCl_3}$ cm^{-1}
51	-15.6 (25)	$C_{48}H_{81}N_5O_8S \cdot {}^3/_4H_2O$ (881.586)	C:65.39 H:7.15 N:7.94 S:3.64	C:65.63 H:7.41 N:7.85 S:3.39	3400, 3340, 1668, (1635), 1600, 1585, 1511, 1460, 1440
52	-26.0 (21)	$C_{42}H_{57}N_5O_6S \cdot {}^1/_2H_2O$ (768.990)	C:65.60 H:7.60 N:9.11 S:4.17	C:65.66 H:7.68 N:9.08 S:3.89	3480, 3340, 1670, 1598, 1508, (1525), 1448, 1425, 1410

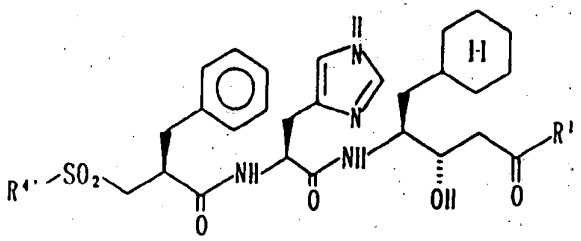
Table 10



(I A)

Coapd. of Ex. No.	R'	R''	Yield %	[α]D° (C=1.0, MeOH) (℃)	Molecular formula	Elemental analysis Calcd.	Elemental analysis Found	I R νmax cm⁻¹
2	phenyl	tert-butyl	75	-22.2° (24℃)	$C_{37}H_{50}N_4O_6S \cdot 1/2H_2O$, $1/4iPr_2O$	C:64.82 H: 7.70 N: 7.85 S: 4.49	C:64.87 H: 7.65 N: 7.99 S: 4.33	3460, 3360(br), 1663, 1600, 1580, 1498, 1450, 1116
3	o-fluorophenyl	tert-butyl	90	-20.9 (24.0)	$C_{37}H_{49}FN_4O_6S \cdot 3/4H_2O$	C:62.56 F: 2.67 H: 7.17 N: 7.89 S: 4.51	C:62.65 F: 2.71 H: 7.12 N: 8.05 S: 4.56	3460, 3360(br), 1666, 1611, 1575, 1480, 1453, 1116
4	m-methoxyphenyl	tert-butyl	73	-18.1 (24.5)	$C_{38}H_{52}N_4O_7S \cdot 1.5H_2O$	C:62.02 H: 7.53 N: 7.61 S: 4.36	C:62.05 H: 7.16 N: 7.52 S: 4.12	3468, 3348(br), 1668, 1600, 1585, 1499, 1464, 1451, 1430, 1289, 1258, 1169, 1117, 1077.
5	p-methylphenyl	tert-butyl	94	-21.3 (24.0)	$C_{38}H_{52}N_4O_6S \cdot 3/4H_2O$	C:64.61 H: 7.63 N: 7.93 S: 4.54	C:64.65 H: 7.64 N: 7.99 S: 4.61	3460, 3350(br), 1666, 1608, 1564, 1498, 1450, 1116
6	2,4-difluoro-phenyl	tert-butyl	93	-21.0 (23.5)	$C_{37}H_{48}F_2N_4O_6S \cdot 1/2H_2O$	C:61.39 F: 5.25 H: 6.82 N: 7.74 S: 4.43	C:61.18 F: 5.35 H: 6.82 N: 7.76 S: 4.40	3470, 3350(br), 1665, 1612(1595sh), 1498, 1450, 1430, 1116, 1100, 970, 855

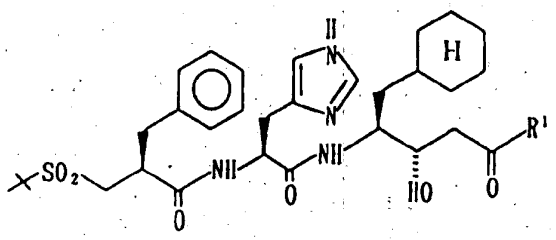
Table 10 (continued)



(I A)

Compd. of Ex. No.	R¹	R⁴'	Yield %	[α]D (C=1.0, MeOH) (℃)	Molecular formula	Elemental analysis		I R νmax cm⁻¹
						Calcd.	Found	
7	1-naphthyl	tert-butyl	60	-15.3 (24.0)	$C_{41}H_{52}N_4O_6S \cdot 5/4H_2O$	C:65.53 H: 7.31 N: 7.46 S: 4.27	C:65.43 H: 7.09 N: 7.37 S: 4.24	3672, 3352(br), 1665, 1605, 1509, 1464, 1450, 1441, 1369, 1291, 1117, 1077
8	3-thienyl	tert-butyl	94	-24.4 (28.0)	$C_{35}H_{48}N_4O_6S_2 \cdot H_2O$	C:59.81 H: 7.17 N: 7.97 S: 9.12	C:59.68 H: 7.02 N: 8.23 S: 9.10	3460, 3350(br), 1662, 1600, 1505, 1446, 1113
9	2-thiazolyl	tert-butyl	71		$C_{34}H_{47}N_5O_6S_2 \cdot 2H_2O \cdot 1/2C_4H_8O_2$	C:56.45 H: 7.24 N: 9.16 S: 8.37	C:56.41 H: 6.95 N: 9.14 S: 8.09	3660, 3356(br), 1661, 1599, 1511, 1446, 1113

Table 10 (continued)



(I A)

Compd. of Ex. No.	R^1	Yield %	$[\alpha]_D^{\cdot}$ C=1.0, MeOH (℃)	Molecular formula	Calcd.	Found	I R νmax cm^{-1}
10	m-fluorophenyl	88	-21.4 (24.0)	$C_{37}H_{49}N_4FO_6S$ $3/4H_2O$	C:62.56 F: 2.67 H: 7.17 N: 7.89 S: 4.51	C:62.72 F: 2.60 H: 7.14 N: 7.67 S: 4.60	3470. 3340. 1663. 1605. 1590. 1496. 1445. 1400. 1370. 1115. 1075. 1015
11	p-fluorophenyl	87	-21.3 (24.0)	$C_{37}H_{49}N_4FO_6S$ $3/4H_2O$	C:62.56 F: 2.67 H: 7.17 N: 7.89 S: 4.51	C:62.60 F: 2.66 H: 7.17 N: 7.84 S: 4.62	3470. 3340. 1665. 1600. 1505. 1450. 1410. 1370. 1156. 1115. 1076
12	2,6-difluoro-phenyl	75	-23.4 (23.5)	$C_{37}H_{48}N_4F_2O_6S$ $2/3H_2O$	C:61.15 F: 5.23 H: 6.84 N: 7.71 S: 4.41	C:61.05 F: 5.26 H: 6.60 N: 7.77 S: 4.75	3468. 3360. 1664. 1624. 1502. 1467. 1450. 1402. 1370. 1290. 1117. 1078. 1016. 991

Table 10 (continued)

Compd. of Ex. No.	R'	Yield %	$[\alpha]_D^{\circ}$ C=1.0, MeOH (℃)	Molecular formula	Calcd.	Found	I R νmax cm^{-1}
13	o-methoxyphenyl	75	- 3.3 (24.0)	$C_{38}H_{52}N_4O_7S \cdot 3/4H_2O$	C:63.18 H: 7.46 N: 7.76 S: 4.44	C:63.18 H: 7.52 N: 7.38 S: 4.03	3468, 3348, 1665, 1600, 1502, 1487, 1465, 1438, 1289, 1163, 1117, 1077, 1026
14	o-chlorophenyl	75	- 8.4 (23.5)	$C_{37}H_{49}ClN_4O_6S \cdot 0.1\ ClH_2Cl_2 \cdot 1/3H_2O$	C:61.23 Cℓ: 5.85 H: 6.91 N: 7.70 S: 4.41	C:61.03 Cℓ: 5.63 H: 6.85 N: 7.68 S: 4.31	3468, 3360, 1665, 1593, 1500, 1450, 1434, 1402, 1370, 1291, 1117, 1077
15	m-cyanophenyl	92	-20.6 (24.5)	$C_{38}H_{49}N_5O_6S \cdot H_2O \cdot 1/4ClH_2Cl_2$	C:61.82 H: 6.99 N: 9.42 S: 4.31	C:61.87 H: 6.75 N: 9.40 S: 4.25	3468, 3360, 2236, 1666, 1602, 1499, 1450, 1431, 1401, 1370, 1288, 1150, 1117, 1077, 909
16	p-methylsulfonylaminophenyl	86	-11.4 (24.0)	$C_{38}H_{53}N_5O_8S_2 \cdot 1/4(iPr)_2O \cdot 1/2H_2O$	C:58.82 H: 7.19 N: 8.68 S: 7.95	C:58.54 H: 7.06 N: 8.46 S: 7.71	3464, 3352, 1664, 1607, 1578, 1492, 1452, 1400, 1340, 1289, 1155, 1117, 1077, 968, 917
17	p-trifluorometylphenyl	95	-18.8 (24.0)	$C_{38}H_{49}F_3N_4O_6S \cdot 1/2H_2O$	C:60.38 F: 7.54 H: 6.67 N: 7.41	C:60.27 F: 7.53 H: 6.77 N: 7.27 S: 4.24	3450, 3350, 1665, 1605, 1510, 1450, 1410, 1325, 1170, 1135, 1115, 1065 S: 4.41

Table 10 (continued)

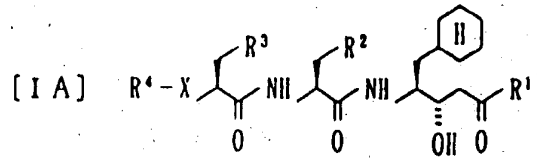
(I A)

Compd. of Ex. No.	R'	R''	Yield %	$[\alpha]_D^{25}$ (C=1.0, MeOH)	Molecular formula	Calcd.	Found	IR ν max cm^{-1}
18	3-morpholino-carbonyloxyphenyl	tert-butyl	92	-15.8±0.6 (25℃)	$C_{42}H_{57}N_5O_9S$ ·1 3/4 H_2O	C:60.09 H: 7.26 N: 8.34 S: 3.82	C:59.93 H: 6.94 N: 8.38 S: 3.79	3470.3320.1711.1680. 1665.1605.1587.1500. 1420.1370.1116.1068
19	3-morpholino-carbonylphenyl	tert-butyl	79	-15.8±0.6 (25℃)	$C_{42}H_{57}N_5O_8S$ ·5/4 H_2O	C:61.93 H: 7.36 N: 8.60 S: 3.94	C:61.70 H: 7.10 N: 8.42 S: 3.92	3356.1665.1627.1581. 1498.1463.1451.1369. 1289.1117.1075.1028
20	3,4-methylene-dioxyphenyl	tert-butyl	88	-16.8±0.6 (25℃)	$C_{53}H_{68}N_4O_{13}S$ ·2H_2O · 2/5 dioxane	C:59.89 H: 7.26 N: 7.05 S: 4.04	C:59.86 H: 6.92 N: 6.77 S: 3.87	3470.3340.1665.1605. 1505.1490.1445.1117. 1080.1042

Table 10 (continued)

Compd. of Ex. No.	R'	R''	Yield %	$[\alpha]_D^{\circ}$ (C=1.0, MeOH)	Molecular formula	Calcd.	Found	IR νmax cm^{-1}
21	cyclohexyl	tert-butyl	94	-21.2±0.6 (24℃)	$C_{37}H_{56}N_4O_8S$ ·1/2H_2O	C:62.42 H: 8.35 N: 7.87 S: 4.50	C:62.42 H: 8.06 N: 8.10 S: 4.33	3460, 3340, 1662(sh1685), 1605, 1500, 1450, 1115
22	p-methoxyphenyl	tert-butyl	91	-16.9±0.6 (24℃)	$C_{38}H_{52}N_4O_7S$ ·2.5H_2O · 1/2 dioxan	C:60.21 H: 7.71 N: 7.02 S: 4.02	C:60.24 H: 7.38 N: 6.78 S: 3.77	3470, 3340, 1665, 1603, 1575, 1510, 1170, 1116, 1076, 1030
37	phenyl	isopropyl	93	-21.2±0.6 (24℃)	$C_{36}H_{48}N_4O_8S$ ·H_2O	C:63.32 H: 7.38 N: 8.20 S: 4.69	C:63.59 H: 7.46 N: 8.01 S: 4.48	3460, 3340, 1665, 1600, 1580, 1500, 1450, 1120,
38	phenyl	ethyl	89	-22.1±0.6 (24℃)	$C_{36}H_{46}N_4O_8S$ ·3/4H_2O	C:63.28 H: 7.21 N: 8.43 S: 4.83	C:63.17 H: 7.18 N: 8.49 S: 4.60	3400, 3350, 1665, 1600, 1582, 1510, 1450, 1310, 1123

Table 10 (continued)

[IA] 

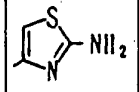
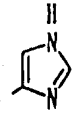
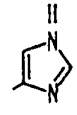
Compd. of Ex. No.	R^1	R^2	R^4	X	Yield%	$[\alpha]_D^0$ (C=1.0, MeOH) (Temp. ℃)	Molecular formula	Calcd.	Found	IR ν max cm^{-1}
28	m-(N-methyl)-aminophenyl		N-morpholino-sulfonyl	NH	52	-25.5 (25)	$C_{37}H_{50}N_6O_7S_2$ ·2/3H_2O· 2/5CH_2Cl_2	C:56.09 H: 6.56 N:10.49 S: 8.01	C:56.16 H: 6.33 N:10.24 S: 7.64	3380. 1667. 1604. 1584. 1508. 1454. 1448. 1410. 1339. 1294. 1261. 1156. 1113. 1071
33	phenyl		ter-butyl-sulfonyl	CH_2	44	-24.9 (23.5)	$C_{38}H_{50}N_4O_6S_2$ ·1/4H_2O (157·159°)	C:62.11 H: 7.12 N: 7.83 S: 8.96	C:62.10 H: 7.24 N: 7.95 S: 8.70	3490. 3400. 1665. 1605. 1580. 1510. 1450. 1115
40	phenyl		N-morpholino-carbonyl	CH_2	79	-15.8 (25)	$C_{42}H_{51}N_5O_6$ ·2H_2O· 2/5CH_2Cl_2	C:64.31 H: 7.10 N: 8.84	C:64.38 H: 6.82 N: 8.97	3460. 3400. 3310. 1662. 1630. 1600. 1580. 1510. 1490. 1450. 1115. 1070
42	4-pyridyl		N-morpholino-carbonyl	CH_2	79	-19.3 (25)	$C_{41}H_{50}N_6O_6$ ·H_2O·1/2;Pr_2O	C:66.73 H: 7.51 N:10.61	C:66.54 H: 7.54 N:10.66	3460. 3400. 3320. 1660(sh1690). 1625. 1520. 1490. 1460. 1445. 1410. 1115

Table 10 (continued)

Compd. of Ex. No.	NMR(δ):
2	0.70~1.83(13H, m), 1.33(9H, s), 2.68~3.18(7H, m), 3.27(1H, m), 3.60(1H, dd, J=9.8, 13.2Hz), 3.80(1H, br), 3.99(1H, m), 4.21(1H, m), 4.60(1H, m), 6.48(1H, d, J=9.4Hz), 6.89(1H, s), 7.08~7.63(8H, m), 7.50(1H, d, J=1.8Hz), 7.93(2H, d, J=8.4Hz)
3	0.68~1.83(13H, m), 1.33(9H, s), 2.70~3.17(7H, m), 3.60(1H, dd, J=13.1, 9.9Hz), 3.59(2H, brs), 3.25(1H, m), 3.98(1H, m), 4.18(1H, m), 4.59(1H, ddd, J=6.8, 6.8, 6.8Hz), 6.51(1H, d, J=9.0Hz), 6.90(1H, s), 7.05~7.37(7H, m), 7.52(1H, m), 7.55(1H, s), 7.84(1H, ddd, J=7.7, 1.9Hz)
4	0.70~1.83(13H, m), 1.32(9H, s), 2.74~3.17(7H, m), 3.27(1H, m), 3.59(1H, dd, J=10.13Hz), 3.83(3H, s), 4.00(1H, m), 4.20(1H, m), 4.60(1H, ddd, J=7.7, 7Hz), 4.72(1H, bs), 6.60(1H, d, J=9Hz), 6.86(1H, s), 7.04~7.55(9H, m), 7.48(1H, s)

Table 10 (continued)

Compd. of Ex. No.	NMR(δ):
5	0.70～1.85(13H, m), 1.32(9H, s), 2.40(3H, s), 2.70～3.18(7H, m), 3.27(1H, m), 3.61(1H, dd, J=13.2, 9.8Hz), 3.75(2H, bs), 3.99(1H, m), 4.19(1H, m), 4.61(1H, ddd, J=6.5, 6.5, 6.5Hz), 6.53(1H, d, J=9.1Hz), 6.88(1H, s), 7.10～7.45(7H, m), 7.52(1H, s), 7.82(2H, d, J=8.2Hz)
6	0.70～1.80(13H, m), 1.34(9H, s), 2.77～3.16(7H, m), 3.20(2H, bs), 3.25(1H, m), 3.59(1H, dd, J=13.95Hz), 3.48(1H, m), 4.18(1H, m), 4.59(1H, ddd, J=7, 7, 7Hz), 6.46(1H, d, J=9.3Hz), 6.78～7.00(2H, m), 6.91(1H, s), 7.23(5H, m), 7.54(1H, s), 7.91(1H, ddd, J=8.6, 8.6, 6.6Hz)
7	0.70～1.85(13H, m), 1.30(9H, s), 2.82(1H, dd, J=13.2, 8.4Hz), 2.90～3.18(6H, m), 3.28(1H, m), 3.59(1H, dd, J=13.0, 10.0Hz), 4.03(1H, m), 4.24(1H, m), 4.60(1H, ddd, J=5, Hz), 5.30(1H, brs), 6.63(1H, d, J=9.2Hz), 6.83(1H, s), 7.20(5H, m), 7.50(4H, m), 7.90(2H, m), 7.86(1H, s), 8.60(1H, d, J=7.6Hz)
8	0.70～1.85(13H, m), 1.33(9H, s), 2.77～3.18(7H, m), 3.26(1H, m), 3.59(1H, dd, J=13.2, 10.2Hz), 3.97(1H, m), 4.18(1H, m), 4.58(1H, m), 6.44(1H, d, J=9.4Hz), 6.88(1H, s), 7.12～7.47(6H, m), 7.50(1H, s), 7.51(1H, dd, J=5.0, 1.2Hz), 8.13(1H, dd, J=1.2, 3Hz)
9	0.70～1.83(13H, m), 1.34(9H, s), 2.74～3.32(8H, m), 3.61(1H, dd, J=12.8, 9.4Hz), 3.73(2H, bs), 3.95(1H, m), 4.23(1H, m), 4.60(1H, ddd, J=6.6, 6.6, 6.6, 6.6Hz), 6.51(1H, d, J=9.2Hz), 6.96(1H, s), 7.12～7.35(5H, m), 7.57(1H, s), 7.68(1H, d, J=3Hz), 8.00(1H, d, J=3Hz)

Table 10 (continued)

Compd. of Ex. No.	(IA) NMR(δ)
10	0.70~1.82(13H, m), 1.33(9H, s), 2.75~3.19(7H, m), 3.28(1H, m), 3.62(1H, dd, J=13.10Hz), 4.02(1H, m), 4.20(1H, m), 4.59(1H, ddd, J=6.4, 6.4, 6.4Hz), 6.55(1H, d, J=9.4Hz), 6.92(1H, s), 7.25(6H, m), 7.45(2H, m), 7.56(1H, s), 7.62(1H, m), 7.70(1H, d, J=7.6Hz)
11	0.70~1.82(13H, m), 1.33(9H, s), 2.75~3.20(7H, m), 3.28(1H, m), 3.57(2H, bs), 3.60(1H, dd, J=13.10Hz), 4.00(1H, m), 4.19(1H, m), 4.59(1H, ddd, J=6.6.6.6.6.6Hz), 6.54(1H, d, J=9.2Hz), 6.90(1H, s), 7.14(2H, dd, J=17.2.8.8Hz), 7.26(6H, m), 7.48(1H, d, J=8Hz), 7.54(1H, s), 7.96(2H, dd, J=9.5.4Hz)
12	0.70~1.85(13H, m), 1.33(9H, s), 2.78~3.18(7H, m), 3.25(1H, m), 3.61(1H, dd, J=13.2.9.8Hz), 3.95(1H, m), 4.12(1H, m), 4.58(1H, ddd, J=6.4.6.4.6.4Hz), 5.68(2H, bs), 6.55(1H, d, J=9.4Hz), 6.85(1H, s), 6.93(2H, t, J=8.2Hz), 7.15~7.48(7H, m), 7.49(1H, s)
13	0.70~1.82(13H, m), 1.33(9H, s), 2.75~3.35(8H, m), 3.62(1H, dd, J=14, 10Hz), 3.87(3H, s), 3.95(1H, m), 4.15(1H, m), 4.62(1H, ddd, J=6.5.6.5.6.5Hz), 6.66(1H, d, J=9.4Hz), 6.82(1H, s), 6.85(2H, m), 7.24(5H, m), 7.46(1H, s), 7.46(1H, td, J=7.8.1.8Hz), 7.70(1H, dd, J=7.8.1.8Hz)

Table 10 (continued)

Compd. of Ex. No.	(IA) NMR(δ)
14	0.70~1.80(13H, m), 1.33(9H, s), 2.78~3.17(7H, m), 3.26(1H, m), 3.52(1H, dd, J=13.9.8Hz), 3.97(1H, m), 4.13(1H, m), 4.57(1H, ddd, J=6.7.6.7.6.7Hz), 6.52(1H, d, J=9.0Hz), 6.85(1H, s), 7.14~7.42(8H, m), 7.46(1H, s), 7.53(1H, m).
15	0.70~1.80(13H, m), 1.33(9H, s), 2.77~3.18(7H, m), 3.29(1H, m), 3.61(1H, dd, J=12.8.9.8Hz), 4.04(1H, m), 4.22(1H, m), 4.57(1H, ddd, J=5.8.5.8.5.8Hz), 6.59(1H, d, J=9Hz), 6.91(1H, s), 7.23(5H, m), 7.56(1H, s), 7.58(1H, t, J=7.8Hz), 7.81(1H, d, J=7.8Hz), 8.14(1H, d, J=8Hz), 8.23(1H, s)
16	0.70~1.82(13H, m), 1.33(9H, s), 2.75~3.17(7H, m), 3.26(1H, m), 3.59(1H, dd, J=13.10.4Hz), 4.01(1H, m), 4.16(1H, m), 4.57(1H, ddd, J=6.4.6.4.6.4Hz), 6.59(1H, d, J=9.2Hz), 6.88(1H, s), 7.20(6H, m), 7.49(1H, d, J=1.2Hz), 7.50(2H, m), 7.69(1H, dd, J=8.4.1.2Hz), 7.86(1H, dd, J=8.2.1.2Hz)
17	0.70~1.80(13H, m), 1.32(9H, s), 2.75~3.18(7H, m), 3.27(1H, m), 3.58(1H, dd, J=13.4.10Hz), 4.04(1H, m), 4.21(1H, td, J=7.2.5Hz), 4.57(1H, ddd, J=6.3.6.3.6.3Hz), 6.54(1H, d, J=9.4Hz), 7.25(5H, m), 7.52(1H, d, J=9Hz), 7.71(2H, d, J=8.2Hz), 8.04(2H, d, J=8Hz)

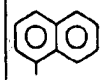
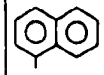
Table 10 (continued)

Compd. of Ex. No.	(IA) NMR(δ)
18	0.70~1.83(13H, m), 1.34(9H, s), 2.70~3.15(7H, m), 3.28(1H, m), 3.48~3.82(8H, m), 3.88(1H, m), 4.14(1H, m), 4.63(1H, ddd, J=6.6, 6.6, 6.6Hz), 6.39(1H, d, J=8.6Hz), 6.80(1H, s), 7.17~7.40(6H, m), 7.40~7.60(3H, m), 7.77(1H, d, J=7.6Hz)
19	0.70~1.80(13H, m), 1.33(9H, s), 2.63~3.17(7H, m), 3.30(1H, m), 3.38~3.95(10H, m), 4.18(1H, m), 4.63(1H, ddd, J=6.6, 6.6Hz), 6.49(1H, d, J=8.8Hz), 6.86(1H, s), 7.23(6H, m), 7.56(1H, s), 7.55(1H, m), 7.71(1H, d, J=6Hz), 7.84(1H, s), 8.00(1H, m)
20	0.70~1.82(13H, m), 1.34(9H, s), 2.78~3.18(7H, m), 3.26(1H, m), 3.60(1H, dd, J=13.9.8Hz), 3.97(1H, m), 4.17(1H, m), 4.60(1H, ddd, J=6.4, 6.4, 6.4Hz), 6.04(2H, s), 6.45(1H, d, J=9.4Hz), 6.84(2H, d, J=8.2Hz), 6.86(1H, s), 7.25(5H, m), 7.39(1H, d, J=1.2Hz), 7.49(1H, s), 7.51(2H, d, J=8.2Hz)

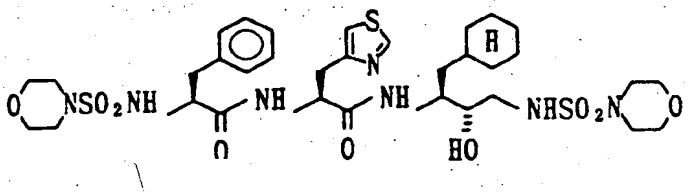
Table 10 (continued)

Compd. of Ex. No.	(IA) NMR(δ)
21	0.70~1.92(23H, ■), 1.35(9H, s), 2.36(1H, ■), 2.55(2H, ■), 2.75~3.18(5H, ■), 3.26(1H, ■), 3.60(1H, dd, J=13.3.9.8Hz), 3.88(1H, ■), 3.99(1H, ■), 4.56(1H, ddd, J=6, 6, 6Hz), 6.41(1H, d, J=9.2Hz), 6.88(1H, s), 7.27(5H, ■), 7.54(1H, s)
22	0.70~0.83(13H, ■), 1.34(9H, s), 2.75~3.17(7H, ■), 3.15(1H, ■), 3.60(1H, dd, J=13.9.6Hz), 3.87(3H, s), 3.98(1H, ■), 4.18(1H, ■), 4.61(1H, ddd, J=6.8, 6.8, 6.8Hz), 6.44(1H, d, J=9.2Hz), 6.86(1H, s), 6.93(2H, d, J=9Hz), 7.25(5H, ■), 7.49(1H, s), 7.91(2H, d, J=8.6Hz)
37	0.70~1.85(13H, ■), 1.23(3H, d, J=6.8Hz), 1.30(3H, d, J=6.8Hz), 2.70~3.18(8H, ■), 3.22(1H, ■), 3.56(1H, dd, J=13.4.9.6Hz), 4.01(1H, ■), 4.20(1H, ■), 4.60(1H, ddd, J=6.6Hz), 6.49(1H, d, J=9.2Hz), 6.87(1H, s), 7.22(5H, ■), 7.50(4H, ■), 7.93(2H, d, J=6.8Hz)
38	0.70~1.85(13H, ■), 1.23(3H, t, J=7.4Hz), 2.65(8H, ■), 3.23(1H, ■), 3.57(1H, dd, J=14, 9.8Hz), 4.03(1H, ■), 4.19(1H, ■), 4.62(1H, ddd, J=6.2, 6.2, 6.2Hz), 6.56(1H, d, J=9.2Hz), 6.88(1H, s), 7.20(5H, ■), 7.45(1H, d, J=1.6Hz), 7.52(3H, ■), 7.93(2H, d, J=6.8Hz)

Table 10 (continued)

Compd. of Ex. No.	R^3	X	[IA] NMR(δ)
28		NH	0.65~1.77(13H, m), 2.50(2H, m), 2.80(3H, m), 2.89(3H, s), 3.00(2H, m), 3.20(1H, dd, J=5.15Hz), 3.40(4H, m), 3.53(1H, dd, J=5.15Hz), 3.95(2H, m), 4.12(1H, m), 4.80(1H, dt, J=4.4, 7.0Hz), 5.18(1H, d, J=6Hz), 6.62(1H, d, J=9.4Hz), 6.82(1H, dt, J=2.2, 7Hz), 7.14(1H, d, J=2Hz), 7.30(8H, m), 8.81(1H, d, J=2Hz), 9.09(1H, d, J=6.8Hz)
33		CH_2	0.70~1.82(13H, m), 1.31(9H, s), 2.83~3.30(9H, m), 3.47(1H, dd, J=4.6, 13.2Hz), 4.01(1H, m), 4.16(1H, dt, J=3, 6.2Hz), 4.60(1H, ddd, J=4.8Hzx3), 5.30(1H, bs), 6.24(1H, s), 6.49(1H, d, J=9.8Hz), 7.25(5H, m), 7.47(2H, t, J=7.4Hz), 7.56(1H, d, J=7Hz), 7.62(1H, d, J=6.8Hz), 7.96(2H, dd, J=1.4, 6.6Hz)
40		CH_2	0.78~1.80(13H, m), 2.56(2H, m), 2.90~3.70(15H, m), 4.04(1H, m), 4.21(1H, m), 4.64(1H, ddd, J=6.2Hz), 6.68(1H, d, J=10Hz), 6.87(1H, s), 7.26~7.59(8H, m), 7.76(1H, d, J=8.2Hz), 7.87(1H, m), 8.02(3H, m),
42		CH_2	0.67~1.77(13H, m), 2.47(1H, dd, J=7.5, 17Hz), 2.62(1H, dd, J=5, 18Hz), 2.88~3.76 (15H, m), 4.08(1H, m), 4.17(1H, m), 4.63(1H, ddd, J=5Hz), 6.77(1H, d, J=10Hz), 6.88(1H, s), 7.29(1H, d, J=7.5Hz), 7.40(1H, t, J=7.5Hz), 7.54(3H, m), 7.80(2H, d, J=6.2Hz), 7.80(2H, m), 8.04(1H, m), 8.33(1H, m), 8.76(2H, d, J=6Hz)

Examples 53



To the compound [25a] (24.5g, 41.6mmol) are added anisole (89.7g, 20eq) and anhydrous dichloromethane (250ml). To the mixture is dropwise added trifluoroacetic acid (250ml) with stirring and ice-cooling over 30 minutes, and the mixture is stirred at room temperature for one hour. The reaction mixture is concentrated in vacuo, made alkaline with Na_2CO_3 and saturated aqueous sodium bicarbonate, and extracted with a mixture of dichloromethane and methanol (9:1). The organic layer is washed with water, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue is subjected to silica gel chromatography (SiO_2: 600g, CH_2Cl_2:MeOH:NH_4OH = 90:10:1) to obtain the compound [26a] (14.63g, 72%).

To the above compound [26a] (11.04g, 22.5mmol) are added N-(morpholinosulfonyl)phenylalanine [12a] (8.5g, 1.2eq), HOBt (3.96g, 1.25eq), and anhydrous CH_3CN (200ml). To the mixture is added DCC (6.05g, 1.3eq) with stirring and ice-cooling, and the mixture is stirred at 0°C for one hour and then at room temperature for an additional one hour. To the reaction mixture is added ethyl acetate and it is then filtered. The filtrate is concentrated in vacuo and subjected to silica gel chromatography (SiO_2: 600g, CH_2Cl_2:MeOH = 97:3). Relevant fractions are combined and treated with isopropyl ether to give the compound [Ib] (16.33g, 92%).

Elemental analysis (as $C_{33}H_{51}N_7O_9S_3 \cdot 0.75H_2O.1.0CH_2Cl_2$)

Calcd.: C: 49.20; H: 6.57; N: 12.13; S 11.90

Found : C: 49.05; H: 6.20; N: 11.92; S 11.78

$[\alpha]_D$=-22.5 (c=1; MeOH; 24°C)

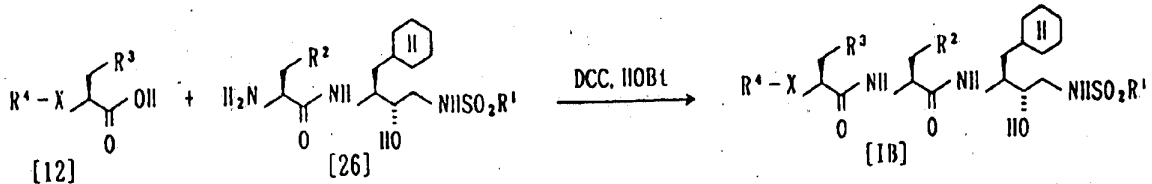
IR: 3370, 2720, 1665, 1530, 1510, 1454, 1340, 1330, 1260, 1155, 1113, 1073, 943

NMR(δ): 0.72(3H,m), 1.12(6H,m), 4.16(1H,bd,J=8Hz), 1.62(3H,bd,J=8Hz), 2.21(1H,bs), 2.47(2H,m), 2.74 (1H, dd,J=10.14Hz), 2.80-3.33(4H,m), 3.21(4H,m),3.33-3.62(8H,m), 3.75(4H,m), 3.97(2H,m), 4.68(1H,m), 5.16 (1H, d,J=5.4Hz), 5.64(1H,t,J=6.8Hz), 6.55(1H,d,J=9.2Hz), 7.19(1H,d,J=1.2Hz), 7.35(5H,m), 8.90(1H,d,J=1.2Hz), 9.40(1H,d,J=6.8Hz)

Examples 54-71

In accordance with substantially the same procedure as disclosed in Example 53, the compounds of the invention listed in Table 11 are obtained.

Table 11



Compd. of Ex. No.	R¹	R²	R³	X	R⁴	[IB] Yield%	[α]D²⁰ C=1, MeOH(℃)	Molecular formula	Elemental analysis Calcd.	Found	IR ν max cm⁻¹
54				NH		82	-38.4 (24.0)	$C_{37}H_{53}N_7O_9S_3 \cdot 0.75H_2O \cdot 0.33(ipr)_2O$	C:53.01 H: 6.75 N:11.10 S:10.89	C:52.83 H: 6.48 N:10.96 S:10.75	3370. 2920. 1730. 1665. 1600. 1530. 1510. 1400. 1340. 1260. 1155. 1115. 1072. 940
55				NH		83	15.3 (24)	$C_{39}H_{55}N_7O_8S_3 \cdot 0.66H_2O \cdot 0.25CH_2Cl_2$	C:55.65 H: 6.76 N:11.57 S: 7.57	C:55.62 H: 6.54 N:11.41 S: 7.18	3340. 2920. 1670. 1600. 1530. 1510. 1505. 1335. 1261. 1155. 1116. 1075
56	-NMe₂			NH		98	-22.9 (25.0)	$C_{31}H_{49}N_7O_8S_3 \cdot 0.5H_2O \cdot 0.25CH_2Cl_2$	C:48.48 H: 6.58 N:12.66 S:12.42	C:48.59 H: 6.48 N:12.28 S:11.37	3370. 2920. 1665. 1604. 1530. 1510. 1400. 1328. 1260. 1153. 1113. 950
57	-NMe₂			NH	+SO₂-	89	-7.4 (24.0)	$C_{32}H_{51}N_5O_7S_3 \cdot 0.2H_2O \cdot 0.1(ipr)_2O$	C:53.80 H: 7.31 N: 9.62 S:13.22	C:53.61 H: 7.25 N: 9.40 S:12.73	3360. 2920. 1660. 1530. 1510. 1448. 1325. 1290. 1145. 1115. 955
58				NH		92	-23.7 (25.0)	$C_{34}H_{47}N_7O_8S_3 \cdot 0.5H_2O \cdot 0.25CH_2Cl_2$	C:50.90 H: 6.05 N:12.13 S:11.90	C:50.96 H: 5.98 N:12.10 S:11.68	3380. 2930. 1665. 1605. 1577. 1530. 1512. 1415. 1340. 1260. 1160. 1115. 1075. 945

Table 11 (continued)

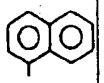
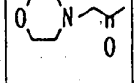
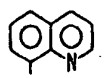
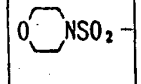
Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[IB] Yield%	$[\alpha]_D^{\circ}$ C=1, MeOH(℃)	Molecular formula	Elemental analysis Calcd.	Found	I R ν max cm^{-1}
59				NH		86	-17.6 (25.0)	$C_{40}H_{51}N_7O_7S_2 \cdot 0.5H_2O \cdot 0.25CH_2Cl_2$	C:57.81 H: 6.33 N:11.72 S: 7.67	C:57.84 H: 6.32 N:11.69 S: 7.55	3330. 2920. 1670. 1599. 1575. 1580. 1505. 1336. 1165. 1115
60				CH_2	$+SO_2-$	70	-15.0 (23.5)	$C_{30}H_{51}N_9O_7S_3 \cdot 0.2H_2O$	C:58.43 H: 6.46 N: 8.74 S:12.00	C:58.20 H: 6.27 N: 8.59 S:11.75	3360. 2920. 1615. 1600. 1567. 1530. 1500. 1450. 1330. 1290
61				CH_2	$+SO_2-$	83	-3.4 (23.5)	$C_{34}H_{48}N_4O_7S_4 \cdot 0.75H_2O$	C:53.28 H: 6.51 N: 7.31 S:16.73	C:53.04 H: 6.22 N: 7.56 S:16.63	3360. 2920. 1660. 1530. 1510. 1450. 1405. 1338. 1290. 1155. 1115. 1015
62				CH_2	$+SO_2-$	72	-3.8 (25.5)	$C_{36}H_{50}N_4O_7S_3 \cdot 0.5H_2O$	C:57.19 H: 6.80 N: 7.41 S:12.72	C:57.01 H: 6.69 N: 7.41 S:12.81	3360. 2920. 1660. 1605. 1530. 1510. 1446. 1330. 1290. 1160. 1165. 1145. 1116. 1115
63				CH_2	$+SO_2-$	88	-5.4 (25.5)	$C_{37}H_{52}N_4O_7S_3$	C:58.39 H: 6.89 N: 7.36 S:12.64	C:58.20 H: 7.08 N: 7.32 S:12.35	3440. 3360. 1662. 1605. 1585. 1510. 1450. 1330. 1290. 1160. 1115. 1095
64				NH		74	-23.5 (25.5)	$C_{35}H_{55}N_7O_9S_3 \cdot 0.75H_2O$	C:50.80 H: 6.88 N:11.85 S:11.02	C:50.98 H: 6.86 N:11.90 S:11.46	3380. 2920. 1665. 1605. 1530. 1510. 1405. 1327. 1260. 1153. 1115. 1070

Table 11 (continued)

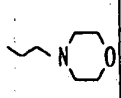
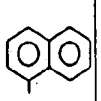
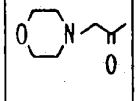
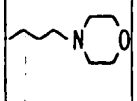
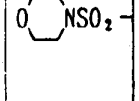
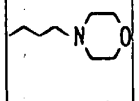
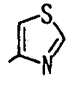
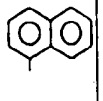
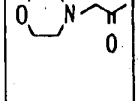
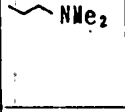
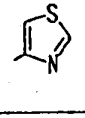
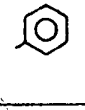
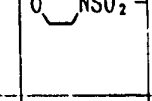
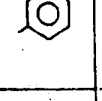
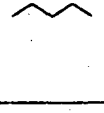
Compd. of Ex. No.	R¹	R²	R³	X	R⁴	[IB] Yield%	[α]D⁰ C=1, MeOH(℃)	Molecular formula	Elemental analysis Calcd.	Found	IR νmax cm⁻¹
65				NH		74	-16.8 (25.5)	$C_{41}H_{50}N_7O_8S_2\cdot H_2O$	C:57.26 H: 7.15 N:11.40 S: 7.45	C:57.12 H: 6.93 N:11.21 S: 7.36	3330. 3000. 1670. 1597. 1525(should). 1507. 1330. 1143. 1124
66				NH		83	-19.9 (25.0)	$C_{30}H_{57}N_7O_9S_3\cdot H_2O\cdot 0.33CH_2Cl_2$	C:49.92 H: 6.88 N:11.22 S:11.00	C:49.76 H: 6.63 N:11.10 S:10.66	3380. 2930. 1665. 1605. 1530. 1510. 1325. 1263. 1155. 1116. 1075. 945
67				NH		86	-14.9 (25.0)	$C_{42}H_{61}N_7O_8S_2\cdot H_2O\cdot 0.5CH_2Cl_2$	C:55.69 H: 7.04 N:10.70 S: 7.00	C:55.48 H: 6.86 N:10.82 S: 6.66	3330. 2920. 1670. 1600. 1530. 1505. 1446. 1330. 1142. 1115
68				NH		80	-23.8 (25.5)	$C_{33}H_{53}N_7O_8S_3\cdot H_2O$	C:50.17 H: 7.02 N:12.41 S:12.17	C:50.08 H: 6.80 N:12.41 S:11.99	3380. 2920. 1665. 1510. 1328. 1262. 1155. 1115
69	CH_3			CH_2	$+SO_2-$	89	-11.1 (24.0)	$C_{31}H_{48}N_4O_7S_3\cdot 0.5H_2O\cdot 0.33CH_2Cl_2$	C:52.51 H: 6.97 N: 7.58 S:13.01	C:52.25 H: 6.80 N: 7.80 S:12.51	3350. 2920. 1660. 1604. 1525. 1510. 1325. 1286. 1146. 1114
70				CH_2	$+SO_2-$	90	-7.0 (23.5)	$C_{34}H_{54}N_4O_7S_3\cdot 0.33H_2O$	C:55.72 H: 7.52 N: 7.64 S:13.12	C:55.58 H: 7.39 N: 7.57 S:12.83	3360. 2920. 1660. 1605. 1530. 1510. 1450. 1325. 1290. 1140. 1115

Table 11 (continued)

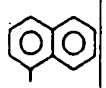
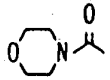
Compd. of Ex. No.	R^1	R^2	R^3	X	R^4	[IB]					
						Yield%	[α]$_D^{20}$ C=1, MeOH(℃)	Molecular formula	Elemental analysis Calcd.	Elemental analysis Found	IR $\nu_{max}^{cm^{-1}}$
71				CH_2		70	-6.6 (24.0)	$C_{39}H_{55}N_5O_7S_2 \cdot 0.75H_2O$	C:59.78 H: 7.27 N: 8.94 S: 8.18	C:59.81 H: 7.10 N: 8.85 S: 7.89	3340. 2930. 1655. 1628. 1530. 1510. 1447. 1326. 1142. 1126

Table 11 (continued)

Compd. of Ex. No.	[IB] NMR δ
54	0.74(3H, m), 1.12(6H, m), 1.42(1H, bd), 1.60(3H, bd, 7.5Hz), 1.95(2H, m), 2.05(1H; bs), 2.52(2H, m), 2.65(2H, m), 3.00(5H, m), 3.21(5H, m), 3.55(2H, m), 3.78(4H, m), 3.88(1H, m), 4.06～4.25(2H, m), 4.74(1H, m), 5.01(1H, d, J=4Hz), 5.62(1H, t, J=7.5Hz), 6.56(1H, d, J=9.2Hz), 7.18(1H, d, J=1.6Hz), 7.45(1H, m), 7.56～7.76(2H, m), 7.87(1H, dd, J=1.4, 8.2Hz), 7.93(1H, dd, J=1, 7.8Hz), 8.23(1H, d, J=8.4Hz), 8.89(1H, d, J=2Hz), 9.61(1H, d, J=6.8Hz)
55	0.76(3H, m), 0.95～1.53(6H, m), 1.60(4H, bd), 1.80(1H, bs), 2.25(2H, m), 2.42(2H, m), 2.80(1H, m), 3.04(4H, m), 3.19(4H, m), 3.46(7H, m), 3.63(1H, m), 3.75(4H, m), 3.92(1H, dd, J=4.3, 14.3Hz), 3.93(1H, m), 4.51(1H, m), 4.70(1H, m), 5.58(1H, bt), 6.81(1H, d, J=9.5Hz), 7.16(1H, d, J=2.0Hz), 7.46(2H, m), 7.59(2H, m), 7.83(2H, m), 7.89(1H, m), 8.16(1H, d, J=8.2Hz), 8.35(1H, d, J=7.0Hz), 8.61(1H, d, J=1.9Hz)
56	0.60～2.00(13H, m), 2.48(2H, m), 2.58(1H, bs), 2.81(6H, s), 2.68～3.12(4H, m), 3.16～3.63(9H, m), 3.97(2H, m), 4.71(1H, m), 5.27(1H, d, J=5.4Hz), 5.52(1H, bt), 6.57(1H, d, J=9.2Hz), 7.20(1H, d, J=1.8Hz), 7.37(5H, m), 8.90(1H, d, J=1.8Hz), 9.37(1H, d, J=6.8Hz)
57	0.70～1.80(13H, m), 1.34(9H, s), 2.79(6H, s), 2.82～3.53(9H, m), 3.67(1H, m), 3.94(1H, m), 4.67(1H, ddd, J=6Hzx3), 5.73(1H, bt), 6.59(1H, d, J=9.4Hz), 7.27(6H, m), 7.53(1H, d, J=6.6Hz), 8.86(1H, d, J=2)
58	0.75(3H, m), 1.13(5H, m), 1.43(1H, m), 1.60(4H, m), 2.52(4H, m), 2.83(5H, m), 3.22(1H, dd, J=5, 15Hz), 3.44(6H, m), 3.87(1H, m), 4.03(1H, m), 4.65(1H, m), 5.33(1H, d, J=5.6Hz), 6.29(1H, t, J=6.3Hz), 6.58(1H, d, J=9.0Hz), 7.16(1H, d, J=1.8Hz), 7.33(6H, m), 7.49(1H, m), 8.20(1H, d, J=8Hz), 8.79(1H, bd), 8.85(1H, d, J=2.0Hz), 9.11(1H, bs), 9.30(1H, d, J=7.0Hz)
59	0.73(3H, bs), 0.92～1.48(6H, m), 1.60(4H, bd), 2.26(2H, m), 2.40(2H, m), 2.73(1H, m), 3.00(4H, m), 3.44(8H, m), 3.85(1H, dd, J=4.2, 14.4Hz), 3.86(1H, m), 4.49(1H, m), 4.63(1H, m), 6.23(1H, bt), 6.80(1H, d, J=9.2Hz), 7.15(1H, d, J=1.6Hz), 7.45(2H, m), 7.58(2H, m), 7.70～7.96(3H, m), 8.16(2H, t, J=9Hz), 8.29(1H, d, J=6.8Hz), 8.58(1H, d, J=1.8Hz), 8.77(1H, m), 9.11(1H, bs)

Table 11 (continued)

Compd. of Ex. No.	[IB] NMR δ
60	0.55～1.70(13H, m), 1.35(9H, s), 2.75(2H, m), 2.85～3.60(8H, m), 3.75(1H, m), 4.55(1H, ddd, J=6.4Hzx3), 6.17(1H, d, J=9.0Hz), 6.79(1H, t, J=6.7Hz), 7.11(1H, d, J=2.0Hz), 7.26(5H, m), 7.55(1H, dd, J=4.3Hz), 7.65(1H, t, J=7.8Hz), 8.05(1H, dd, J=1.4, 8.2Hz), 8.26(1H, dd, J=1.8, 8.3Hz), 8.41(1H, dd, J=1.4, 7.2Hz), 8.58(1H, d, J=2.0Hz), 9.04(1H, dd, J=1.8, 4.3Hz)
61	0.62～1.75(13H, m), 1.34(9H, s), 2.70～3.54(10H, m), 3.62(1H, m), 3.89(1H, m), 4.61(1H, ddd, J=6.4Hzx3), 6.40(1H, t, J=6.8Hz), 6.48(1H, d, J=9.2Hz), 7.07(1H, dd, J=3.6, 5Hz), 7.25(6H, m), 7.40(1H, d, J=6.8Hz), 8.70(1H, d, J=2Hz)
62	1.34(9H, m), 0.63～1.78(13H, m), 2.74(1H, dt, J=6.5, 13.5Hz), 2.85～3.52(8H, m), 3.58(1H, dt, J=3.5, 6.6Hz), 4.59(1H, ddd, J=6.5Hzx3), 6.21(1H, t, J=6.4Hz), 6.42(1H, d, J=9.2Hz), 7.19(1H, J=1.7Hz), 7.25(5H, m), 7.41(1H, d, J=6.8Hz), 7.52(3H, m), 7.87(2H, m), 8.66(1H, d, J=2.0Hz)
63	0.60～1.75(13H, m), 1.34(9H, s), 2.63(3H, s), 2.70(1H, dt, J=6.6, 13.6Hz), 2.80～3.46(9H, m), 3.53(1H, m), 3.87(1H, m), 4.47(1H, ddd, J=5.8Hzx3), 5.89(1H, t, J=7Hz), 6.41(1H, d, J=9Hz), 6.92(1H, s), 7.28(5H, m), 7.52(3H, m), 7.63(1H, d, J=5.8Hz), 7.86(2H, dd, J=1.6, 7.7Hz)
64	0.76(3H, m), 1.13(1.43(1H, bd, J=9Hz), 1.60(4H, bd, J=6Hz), 2.02(1H, bs), 2.52(6H, m), 2.72(1H, dd, J=10, 16Hz), 2.88(5H, bt, J=7Hz), 3.03(2H, m), 3.26(2H, m), 3.45(8H, m), 3.75(4H, t, J=4.7Hz), 3.92(1H, m), 3.98(1H, m), 4.68(1H, m), 5.17(1H, d, J=5.5Hz), 5.70(1H, bt, J=5Hz), 6.50(1H, d, J=9.6Hz), 7.16(1H, d, J=2.0Hz), 7.34(5H, m), 8.87(1H, d, J=2.0Hz), 9.39(1H, d, J=6.9Hz)
65	0.74(3H, m), 0.9～1.35(5H, m), 1.45(1H, d, J=8Hz), 1.60(4H, m), 1.98(1H, bs), 2.24(2H, m), 2.39(2H, m), 2.55(4H, m), 2.80～3.15(8H, m), 3.25(2H, t, J=7Hz), 3.30～3.68(8H, m), 3.75(4H, m), 3.90(1H, dd, J=4.4, 14.5Hz), 3.91(1H, m), 4.50(1H, m), 4.67(1H, m), 5.67(1H, bt), 6.73(1H, d, J=9.2Hz), 7.15(1H, d, J=1.4Hz), 7.46(2H, m), 7.60(2H, m), 7.76(1H, d, J=3.6Hz), 7.84(1H, dd, J=2.6, 6.8Hz), 7.92(1H, m), 8.16(1H, d, J=8.4Hz), 8.34(1H, d, J=7.2Hz), 8.60(1H, d, J=2Hz)

Table 11 (continued)

Compd. of Ex. No.	[1 B]. NMR δ
66	0.55～1.74(13H, m), 2.02(2H, m), 2.18(1H, bs), 2.50(6H, m), 2.66～2.94(3H, m), 2.94～3.30(5H, m), 3.45(8H, m), 3.73(5H, m), 3.90(1H, m), 4.00(1H, m), 4.67(1H, m), 5.20(1H, bd), 5.78(1H, bt), 6.53(1H, d, J=9.4Hz), 7.16(1H, d, J=1.9Hz), 7.35(5H, m), 8.87(1H, d, J=2.0Hz), 9.41(1H, d, J=6.6Hz)
67	0.62～1.75(13H, m), 2.04(2H, m), 2.20(2H, m), 2.39(2H, m), 2.51(6H, m), 2.90(3H, m), 3.10(4H, m), 3.43(6H, m), 3.57(2H, m), 3.73(4H, m), 3.90(2H, m), 4.50(1H, m), 4.69(1H, m), 5.76(1H, bt), 6.77(1H, d, J=9Hz), 7.16(1H, d, J=1.4Hz), 7.44(2H, m), 7.60(2H, m), 7.76(1H, d, J=3.2Hz), 7.85(1H, m), 7.90 (1H, m), 8.16(1H, d, J=8Hz), 8.37(1H, d, J=6.8Hz), 8.60(1H, d, J=2Hz)
68	0.73(3H, m), 1.15(5H, m), 1.43(1H, bd, J=8Hz), 1.61(4H, bd, J=6Hz), 2.31(6H, s), 2.50(2H, m), 2.74 (1H, dd, J=10.14Hz), 2.83(5H, m), 3.04(2H, m), 3.26(2H, m), 3.45(7H, m), 3.90(1H, m), 4.02(1H, dd, J=2.8, 10.4Hz), 4.69(1H, m), 5.23(1H, bs), 6.51(1H, d, J=9Hz), 7.17(1H, d, J=1.6Hz), 7.35(5H, m), 7.35(5H, m), 8.87(1H, d, J=2Hz), 9.32(1H, d, J=7Hz)
69	0.70～1.80(13H, m), 1.35(9H, s), 2.96(3H, s), 2.75(1H, bs), 2.87(～3.50(9H, m), 3.65(1H, m), 3.45 (1H, m), 4.63(1H, ddd, J=5.8Hz), 5.78(1H, t, J=6.6Hz), 6.50(1H, d, J=9.2Hz), 7.28(6H, m), 7.60(1H, d, 6.2Hz), 8.77(1H, d, J=2Hz)
70	0.70～1.88(17H, m), 0.95(3H, t, J=7.2Hz), 2.87～3.52(12H, m), 3.63(1H, m), 3.94(1H, m), 4.63(1H, ddd, J=6.2Hz×3), 5.68(1H, t, J=6.4Hz), 6.45(1H, d, J=9Hz), 7.25(6H, m), 7.54(1H, d, J=6.4Hz), 8.76 (1H, d, J=2Hz)
71	0.64～1.88(17H, m), 0.94(3H, t, J=7.2Hz), 2.28(1H, dd, J=6.4, 16.6Hz), 2.60～3.80(19H, m), 4.04 (1H, m), 4.70(1H, ddd, J=4.7Hz×3), 5.57(1H, t, J=6.8Hz)

R nin inhibition potency of the compounds (I) of th invention was determined in vitro and in vivo according to the procedure described in the following Experiments.

Experiment 1 Potency in vitro

Commercially available lyophilized human plasma (Ortho, Bi-Level Plasma Renin Control) was renatured by dissolving in water. Angiotensinogen was allowed to react with intrinsic renin contained in the renatured plasma to generate angiotensin I (AI), which was quantitatively measured with radioimmunoassay (RIA). Thus, potency of the plasma renin was determined on the basis of the AI production. For this purpose, Renin RIA kit (RENIN' RIABEAD^{R}) manufactured by Dinabott was used. All of the reagents necessary for the measurement of the AI production were available from the attachment of the kit, and the measurement was conducted according to the manufacturer's direction.

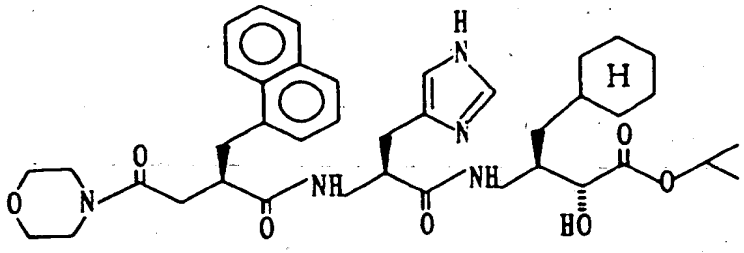
To the plasma (0.2ml) were added all of the reagents, and the mixture was combined with either of sample solutions (0.002ml) of various concentrations which had been prepared by dissolving a test compound in different amount of ethanol. Ethanol (0.002ml) containing no test compound was used as a control solution. The amount of AI produced was measured after 60 minutes incubation. Renin inhibition potency of test compound was determined by comparing the amount of AI produced by a sample solution with that produced by a control solution. The concentrations of the test compounds which inhibit renin activity by 50% (IC_{50}) are summarized in Table 11.

Table 11 Renin Inhibition in vitro

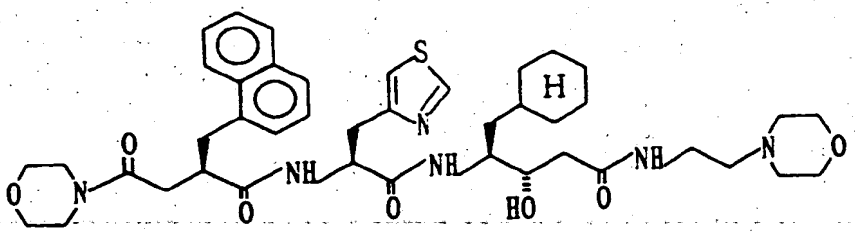
Test Compound (Example No.)	IC_{50}	Test Compound (Example No.)	IC_{50}	Test Compound (Example No.)	IC_{50}
1	6.09	22	39.2	42	13
2	5.87	23	2.07	43	0.51
3	4.44	24	1.56	44	1.53
4	3.21	25	3.17	45	0.31
5	29.0	26	1.32	46	3.16
6	4.22	27	1.78	47	5.90
8	6.17	28	0.52	48	1.98
9	12.0	29	3.31	49	2.34
10	10.9	30	1.07	50	14.8
11	9.1	31	11.6	51	4.51
12	4.56	32	6.72	52	1.69
13	53.9	33	4.65	53	0.36
14	9.3	34	9.53	55	0.60
15	12.6	35	0.63	56	0.70
16	71.3	36	4.98	57	0.80
17	259	37	14.5	58	0.19
18	22.8	38	39.2	59	0.41
19	3.75	39	7.52	62	1.24
20	7.36	40	18.1	64	0.70
21	2.73	41	4.98	69	0.53
				(1)(KRI-1314)	21.3
				(2)(ES-6864)	3.75

IC_{50} : nM

(1) KRI-1314



(2) ES-6864



Experiment 2 Potency in vivo

Crab-eating monkeys (Cynomolgus monkeys) (2.8-5.0 kg) were fed on low sodium diet (Na 7.15mg/100g feed) for six days, during which the monkeys intramuscularly received furosemide (2mg/kg body weight) every other day from the second day of the experiment, in order to make the monkeys hyperrenin condition.

After seven days of low sodium feeding, the monkeys were restrained on a monkey chair. Compounds to be tested are dissolved in 0.1M citric acid/physiological saline or suspended in water with addition of β-cyclodextrin, and orally administered to the monkeys using a stomach probe (15mg/kg body weight). Two milliliters of blood was collected from the femoral vein before administration of the compounds and 0.5, 1.5, 2.5 and 4 hours after the administration. For the blood collection, an injection syringe containing 30μl of 6% aqueous EDTA·2Na solution was used. The collected blood was transferred into a test tube and centrifuged (3000 rpm, 10 minutes) at 4°C, and the resultant supernatant was used to determine the renin content. Plasma renin activity (AI(ng)/ml/h value) was measured using a Radioimmunoassay kit commercially available from Dinabott Co. in the same manner as in the foregoing in vitro test. Renin inhibition potencies of the compounds tested, which were expressed as a percentage of renin activity relative to the activity before the administration, are listed in Table 12.

Table 12

Compound Example No.	Max	Mean	4h	6h	8h	24h
1	33	22	22			
2	49	46	49			
8	60	52	60			
21	55	37	55			
24	99	90	77	56	42	28
26	83	71	69	99		
27	81	65	81	73	64	28
28	97	74	97	89	83	53
33	95	85	68	82		
35	39	30	39	23	24	14
39	46	28	12			
40	44	30	44			
41	95	89	87	76	54	18
43	98	86	95	83	70	11
44	99	97	91	81	71	21
47	59	47	55	6	18	34
48	98	88	88	63	33	0
49	92	84	78	72	51	12
50	93	59	58	42	29	0
51	80	48	35	0	0	0
53	96	85	94		73	
56	93	72	82		85	
57	100	97	89		80	
58	83	71	82		67	

1) Administration rate of compound No. 1 is 30mg/kg.

2) Furosemide was not administered in case of Nos. 2 and 8.

The compounds of the invention which are not listed in Table 12 showed similar inhibition potencies.

Vasodepressor activity of the compounds of the invention was also measured with direct technique using a conscious monkey, where a monkey was administered a compound of the invention orally or intravenously (a solution in Tween 20). The test results are shown in Table 13.

Table 13

Compound Example No.	Administration route	Dose (mg/kg)	Maximum reduced BP (-ΔmmHg)
43	p.o.	100	35
		30	10
		10	5
43	i.v.	3	-
		1	20
		0.3	5
44	i.v.	3	20
		1	8
		0.3	5

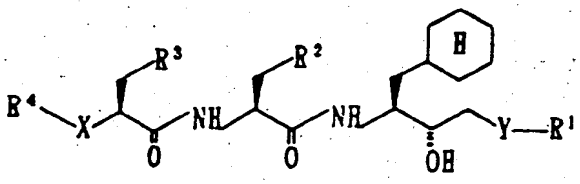
The above test results show that the compounds of the present invention have renin inhibition potency both in vitro and in vivo.

The compounds of the invention are thus useful for the treatment of hypertension due to the renin inhibition when orally administered. However, other administration routes may be also effective.

As discussed previously, the compounds of the invention can be formulated into a pharmaceutical composition together with suitable carriers or excipients. When the compounds of the invention are used as a hypotensive agent, suitable dosage is 0.01-50mg/kg/day in one to three divided does, preferably 0.05-10mg/kg/day, when orally administered, and 1-5000μg/kg/day, preferably 5-500μg/kg/day, when parenterally administered.

Claims

1. A dipeptide derivative of formula (I):



(I)

wherein:

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S-;

R^3 is aryl of 5- or 6-membered heterocyclic radical;

R^4 is $R^{4'}$-SO_2 or $R^{4'}$-CO;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; C_3-C_{10} cycloalkyl, or heterocyclic radical;

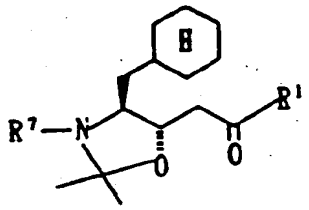
X is CH_2, NH, O, or S; and

Y is CO or $NHSO_2$ wherein R^1, R^2, R^3 and $R^{4'}$ each may b substituted with one to three substituents select d ind pendently from a group consisting of hydroxy; halogen; trifluoromethyl; -CN; heterocyclic radical; C_1-C_6 alkyl; C_3-C_{10} cycloalkyl; -O-C_1-C_6 alkyl; -S-C_1-C_6 alkyl; -SO-C_1-C_6 alkyl; -SO_2-C_1-C_6 alkyl; C_1-C_6 alkylenedioxy; -CO-O-C_1-C_6 alkyl; -NHCO-C_1-C_6 alkyl; -$NHSO_2$-C_1-C_6 alkyl; -NR^5R^6; -O-CO-NR^5R^6; -CO-NR^5R^6; -O-C_1-C_6 alkyl NR^5R^6; R^5 and R^6 are independently hydrogen, formyl or C_1-C_6 alkyl, or R^5 and

R^6, when taken together with the nitrogen to which they are attached, form a cyclic amino group; or an acid addition salt thereof.

2. A compound as claimed in Claim 1 wherein R^2 is optionally substituted 5- or 6-membered heterocyclic group; R^3 is optionally substituted aryl; R^4 is morpholinosulfonyl; and x is NH.

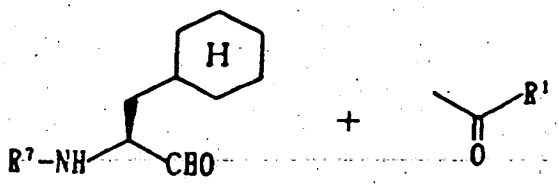
3. A compound for the manufacture of the derivative of formula (I) of Claim 1, said compound having the formula:



wherein, R^1 is as defined in Claim 1, and R^7 is hydrogen or an amino protecting group.

4. A process for the preparation of a compound as defined in Claim 1 of Claim 2 wherein Y is CO comprising at least the final step of the following reaction scheme:

Step 1



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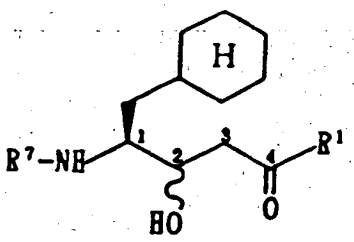

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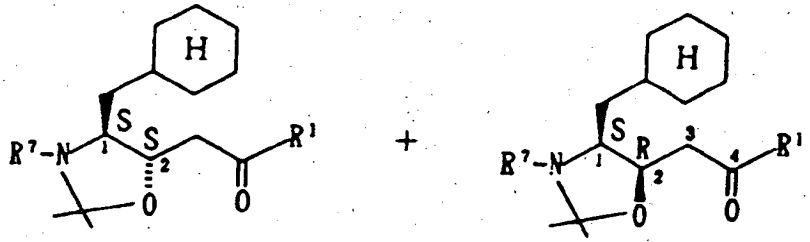

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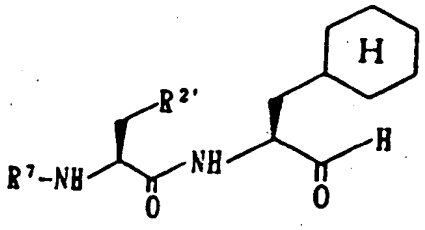
Step 2b



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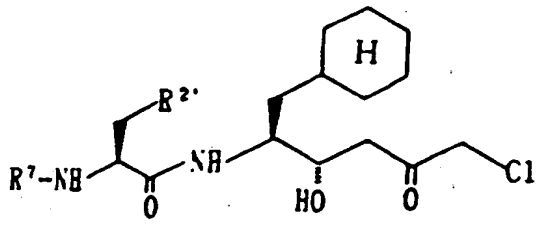
Step 2c



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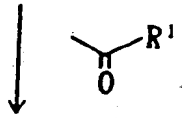

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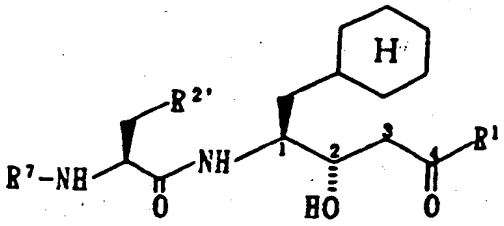

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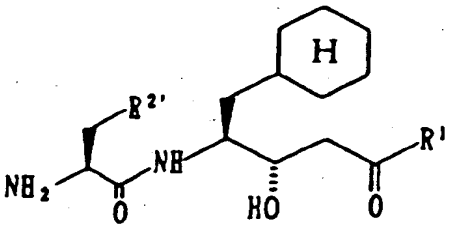
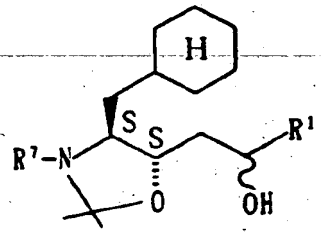
Step 3



[11]

Step 2a

[4]



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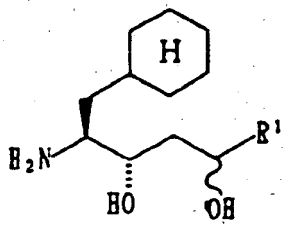

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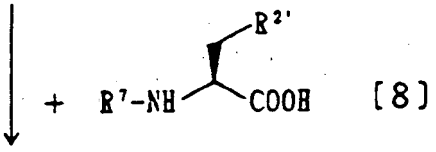

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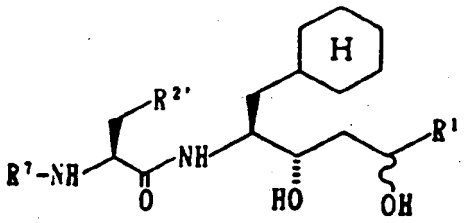

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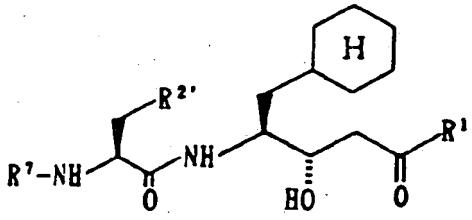
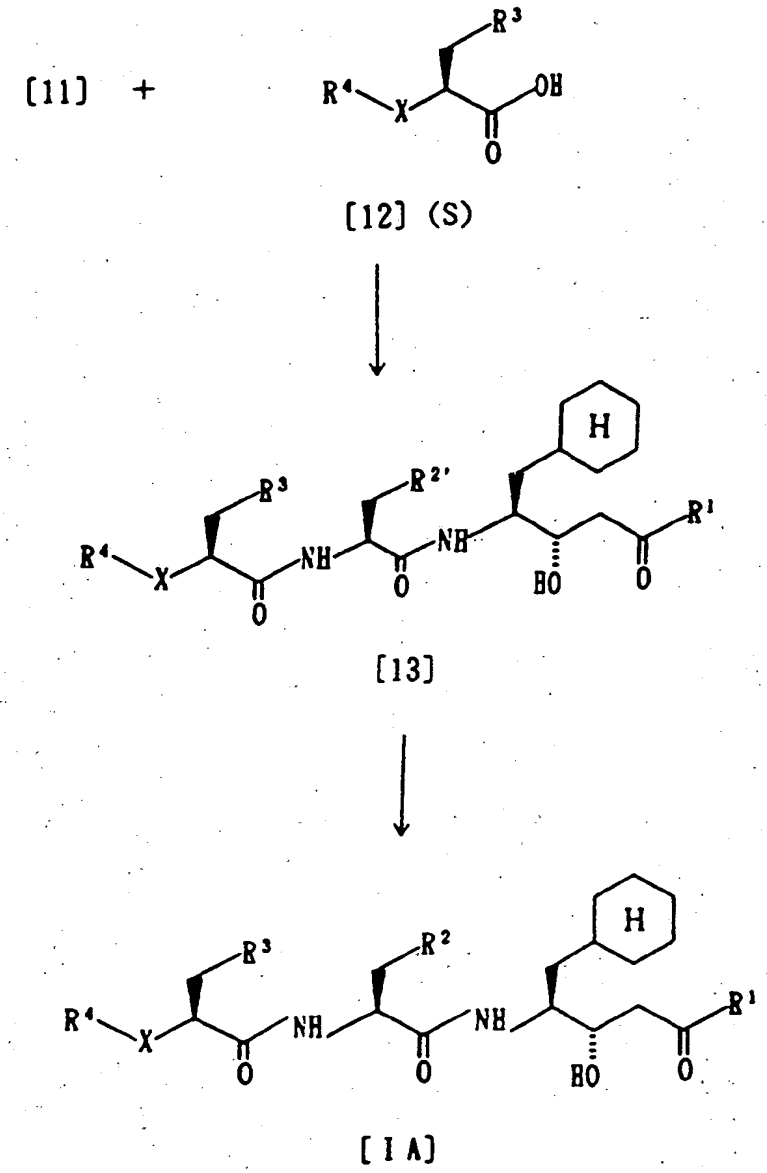


[10]

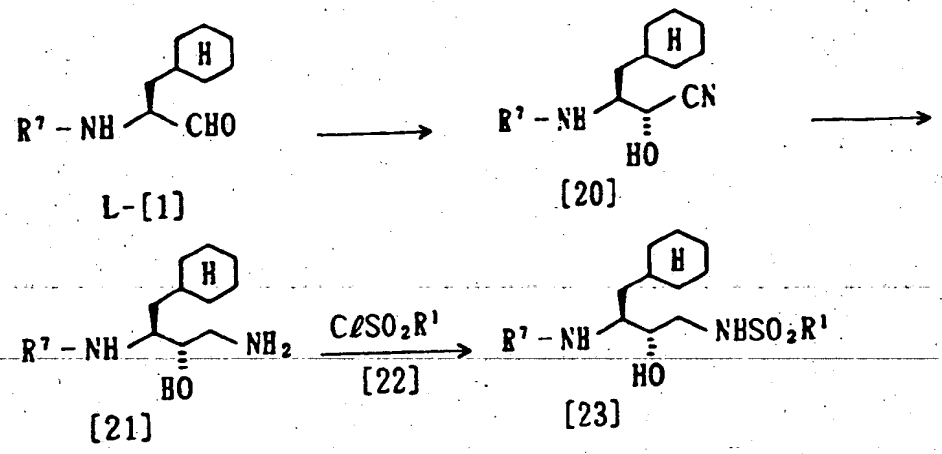
Step 4



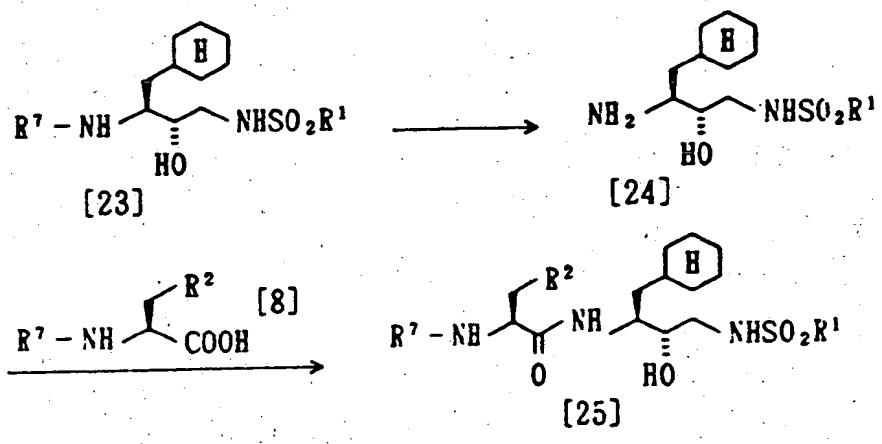
wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1, $R^{2'}$ is protected R^2 and R^7 is an amino protecting group.

5. A process for preparing a compound as defined in Claim 1 or Claim 2 wherein Y is $NHSO_2$ comprising at least the final step of the following reaction scheme:

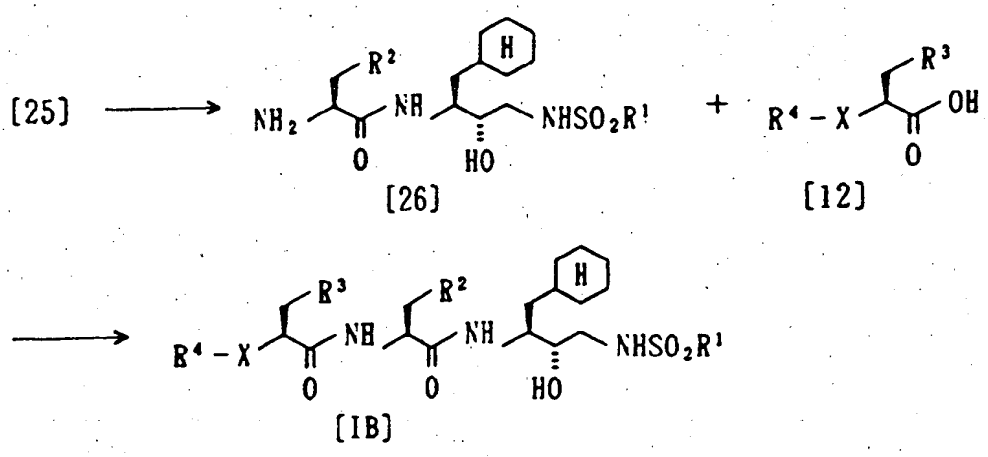
Step 1



Step 2



Step 3



wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1 and R^7 is an amino protecting group.

6. A pharmaceutical preparation for use in the treatment of hypertension comprising a pharmaceutically effective amount of at least one compound as defined in Claim 1 or Claim 2 together with one or more pharmac utically acceptable carriers, diluents or excipients.

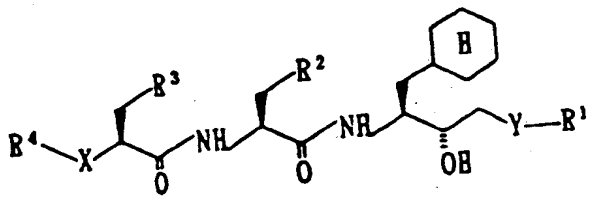
7. The us of a compound as defined in Claim 1 or Claim 2 in the manufacture of a medicament for use in the treatment of hypertension.

8. A process for carrying out a stereo selective aldol condensation between an aldelyde and a ketone wherein the reaction is carried out in the presence of a metal amide and a crown ether in an organic solvent and at a temperature in the range -10 to about -100°C.

9. A process as claimed in Claim 8 wherein the amide is sodium bis-trimethylsilylamide ($NaN(TMS)_2$), the crown ether is 15-crown-5 and the temperature is about -78°C.

Claims for the following Contracting State : ES

1. A process for the production of a pharmaceutical preparation for the treatment of hypertension comprising the step of admixing a pharmaceutically effective amount of at least one compound of the formula



(I)

wherein:

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S-;

R^3 is aryl of 5- or 6-membered heterocyclic radical;

R^4 is $R^{4'}$-SO_2 or $R^{4'}$-CO;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; C_3-C_{10} cycloalkyl, or heterocyclic radical;

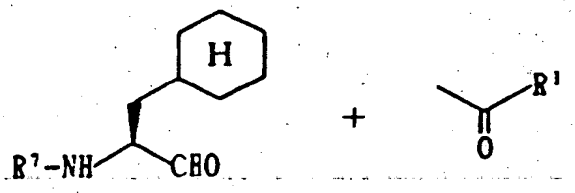
X is CH_2, NH, O, or S; and

Y is CO or $NHSO_2$ wherein R^1, R^2, R^3 and $R^{4'}$ each may be substituted with one to three substituents selected independently from a group consisting of hydroxy; halogen; trifluoromethyl; -CN; heterocyclic radical; C_1-C_6 alkyl; C_3-C_{10} cycloalkyl; -O-C_1-C_6 alkyl; -S-C_1-C_6 alkyl; -SO-C_1-C_6 alkyl; -SO_2-C_1-C_6 alkyl; C_1-C_6 alkylenedioxy; -CO-O-C_1-C_6 alkyl; -NHCO-C_1-C_6 alkyl; -$NHSO_2$-C_1-C_6 alkyl; -NR^5R^6; -O-CO-NR^5R^6; -CO-NR^5R^6; -O-C_1-C_6 alkyl NR^5R^6; R^5 and R^6 are independently hydrogen, formyl or C_1-C_6 alkyl, or R^5 and R^6, when taken together with the nitrogen to which they are attached, form a cyclic amino group; or an acid addition salt thereof together with one or more pharmaceutically acceptable diluents, excipients or carriers.

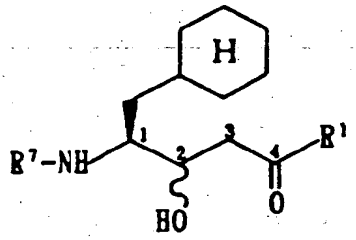
2. A process as claimed in Claim 1 wherein R^2 is optionally substituted 5- or 6-membered heterocyclic group; R^3 is optionally substituted aryl; R^4 is morpholinosulfonyl; and x is NH.

3. A process for the preparation of a compound as defined in Claim 1 of Claim 2 wherein Y is CO comprising at least the final step of the following reaction scheme:

Step 1



[1](S) [2]



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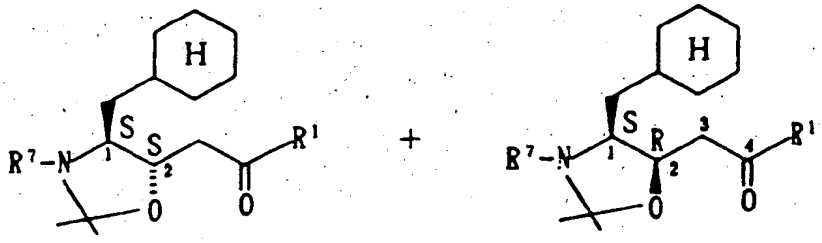

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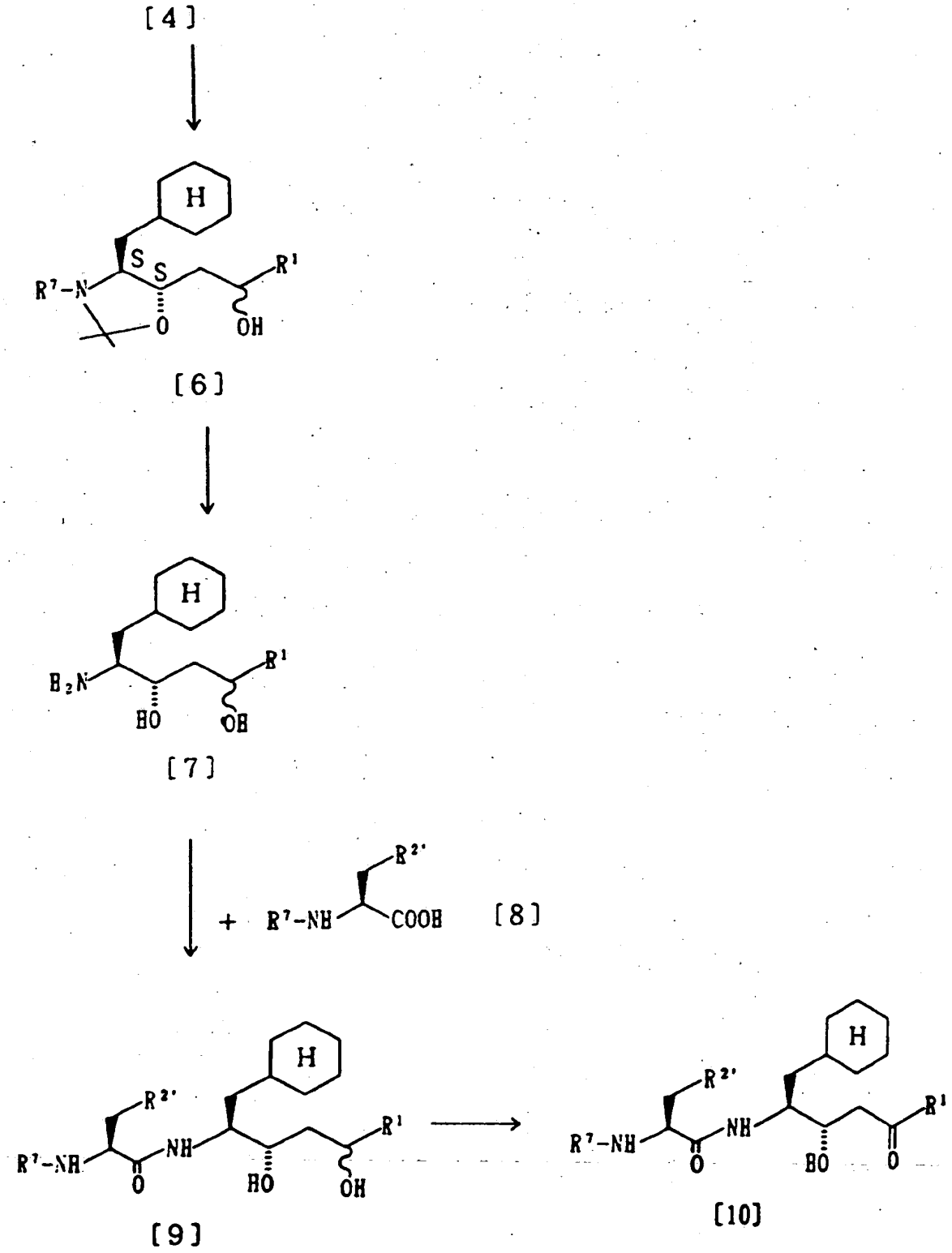
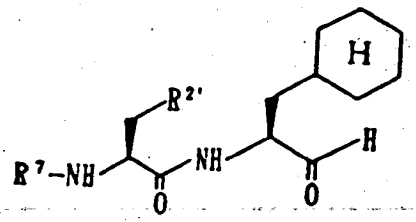
Step 2a

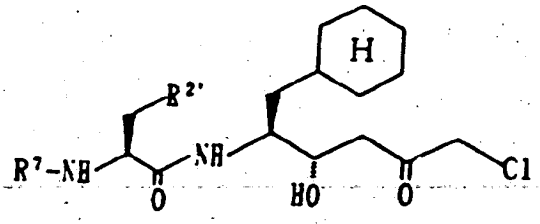

[4]
H
S
S
R¹
R⁷-N
O
OH
[6]
H
R¹
H₂N
HO
OH
[7]
R²'
+ R⁷-NH
COOH
[8]
H
R²'
R⁷-NH
NH
R¹
O
HO
OH
[9]
H
R²'
R⁷-NH
NH
R¹
O
HO
O
[10]

Step 2b



[14]

Step 2c



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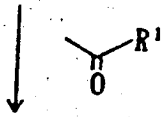

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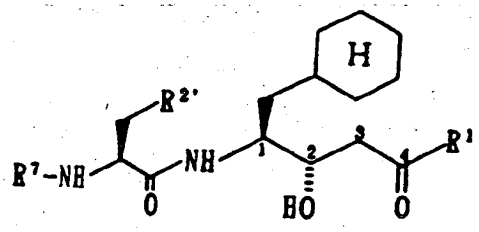

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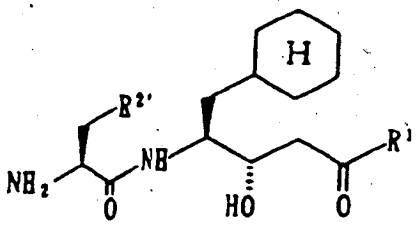
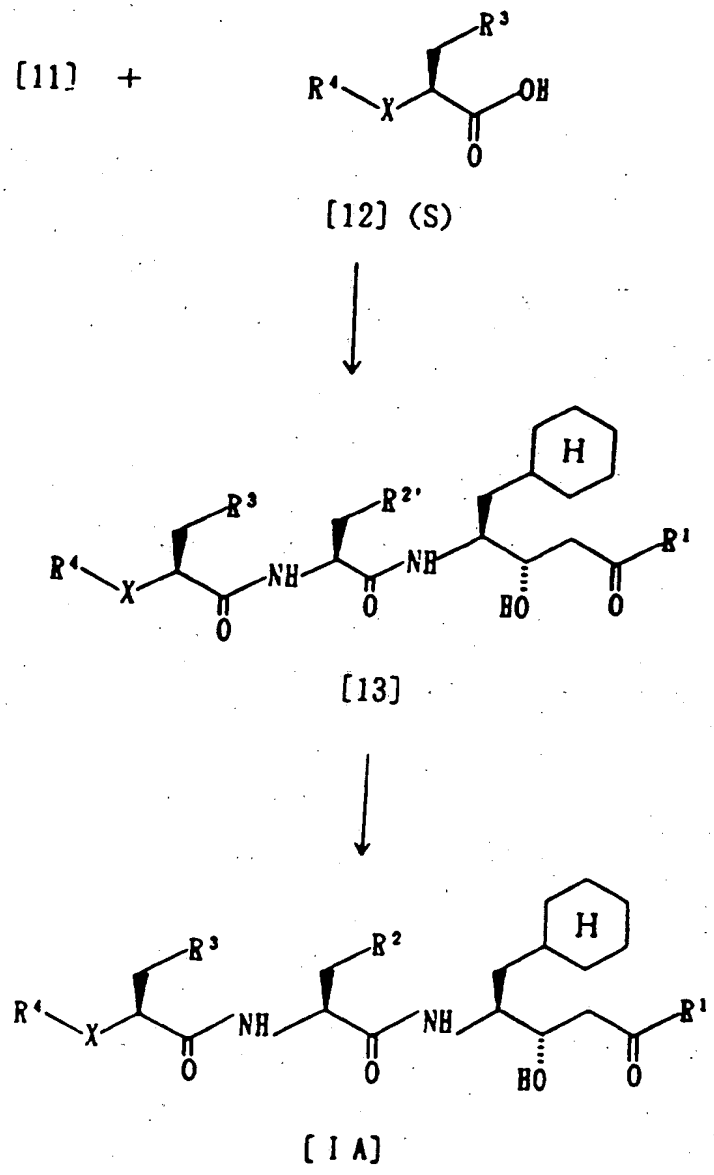
Step 3



[11]

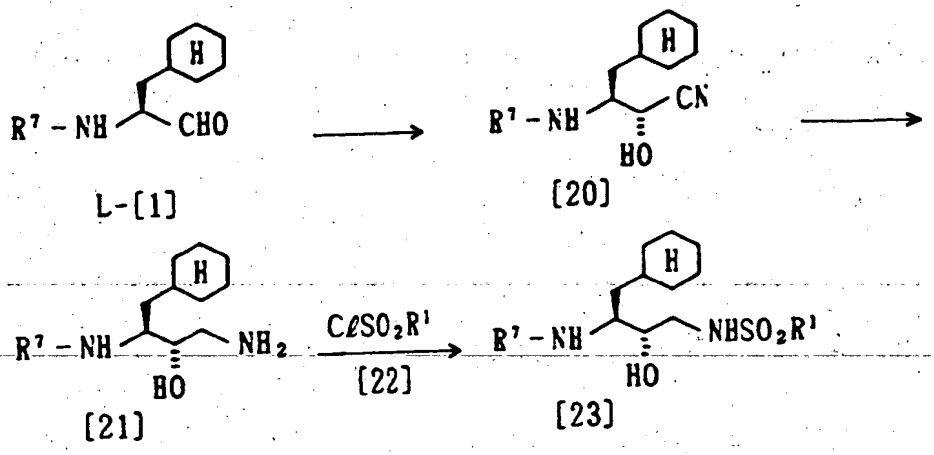
Step 4



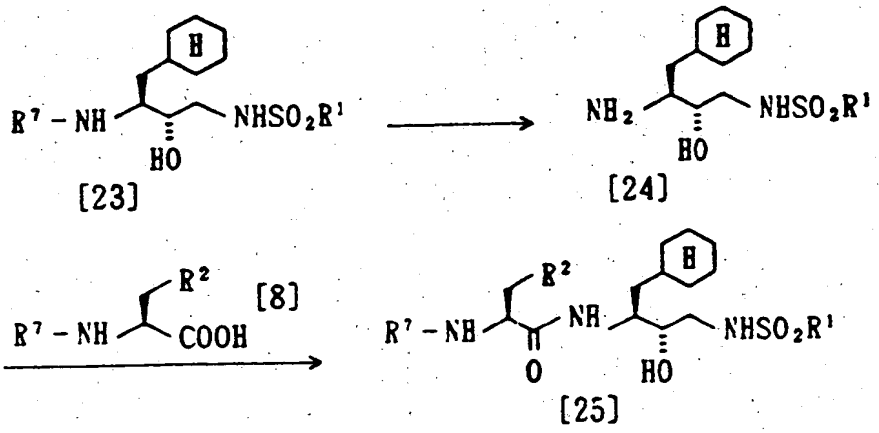
wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1, $R^{2'}$ is protected R^2 and R^7 is an amino protecting group.

4. A process for preparing a compound as defined in Claim 1 or Claim 2 wherein Y is $NHSO_2$ comprising at least the final step of the following reaction scheme:

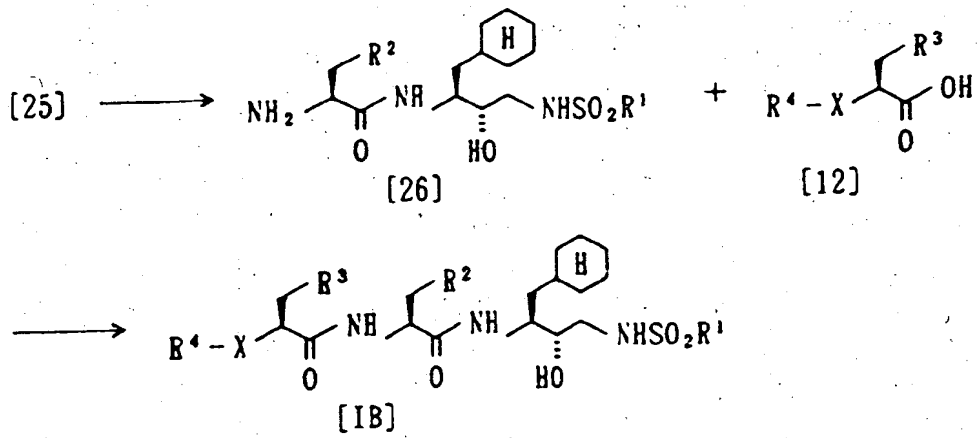
Step 1



Step 2



Step 3



wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1 and R^7 is an amino protecting group.

5. The use of a compound as defined in Claim 1 or Claim 2 in the manufacture of a medicament for use in

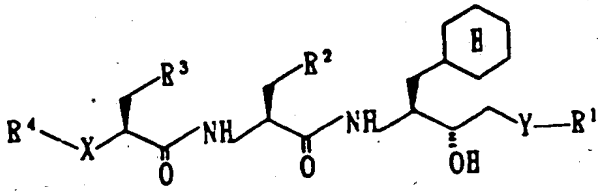
the treatment of hypertension.

6. A process for carrying out a stereo selective aldol condensation between an aldelyde and a ketone wherein the reaction is carried out in the presence of a metal amide and a crown ether in an organic solvent and at a temperature in the range -10 to about -100°C.

7. A process as claimed in Claim 8 wherein the amide is sodium bis-trimethylsilylamide ($NaN(TMS)_2$), the crown ether is 15-crown-5 and the temperature is about -78°C.

Claims for the following Contracting States: GR

1. A process for the production of a pharmaceutical preparation for the treatment of hypertension comprising the step of admixing a pharmaceutically effective amount of at least one compound of the formula



(I)

wherein:

R^1 is C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_{10} cycloalkyl, aryl, or heterocyclic radical;

R^2 is carbamoyl, aryl, 5- or 6-membered heterocyclic radical, C_1-C_{12} alkyl-S-, C_1-C_{12} alkyl-S-CH_2-, or C_3-C_{10} cycloalkyl-S-;

R^3 is aryl of 5- or 6-membered heterocyclic radical;

R^4 is $R^{4'}$-SO_2 or $R^{4'}$-CO;

$R^{4'}$ is aryl, C_1-C_{12} alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl; C_3-C_{10} cycloalkyl, or heterocyclic radical;

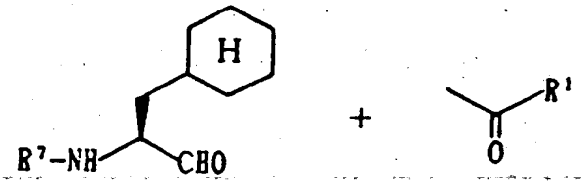
X is CH_2, NH, O, or S; and

Y is CO or $NHSO_2$ wherein R^1, R^2, R^3 and $R^{4'}$ each may be substituted with one to three substituents selected independently from a group consisting of hydroxy; halogen; trifluoromethyl; -CN; heterocyclic radical; C_1-C_6 alkyl; C_3-C_{10} cycloalkyl; -O-C_1-C_6 alkyl; -S-C_1-C_6 alkyl; -SO-C_1-C_6 alkyl; -SO_2-C_1-C_6 alkyl; C_1-C_6 alkylenedioxy; -CO-O-C_1-C_6 alkyl; -NHCO-C_1-C_6 alkyl; -$NHSO_2$-C_1-C_6 alkyl; -NR^5R^6; -O-CO-NR^5R^6; -CO-NR^5R^6; -O-C_1-C_6 alkyl NR^5R^6; R^5 and R^6 are independently hydrogen, formyl or C_1-C_6 alkyl, or R_5 and R_6, when taken together with the nitrogen to which they are attached, form a cyclic amino group; or an acid addition salt thereof together with one or more pharmaceutically acceptable diluents, excipients or carriers.

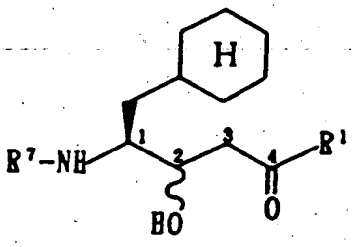
2. A process as claimed in Claim 1 wherein R^2 is optionally substituted 5- or 6-membered heterocyclic group; R^3 is optionally substituted aryl; R^4 is morpholinosulfonyl; and x is NH.

3. A process for the preparation of a compound as defined in Claim 1 of Claim 2 wherein Y is CO comprising at least the final step of the following reaction scheme:

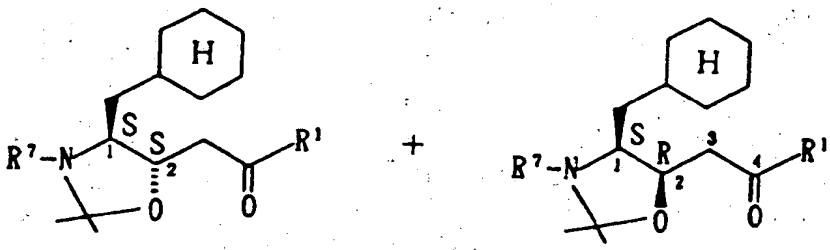
Step 1



[1](S) [2]

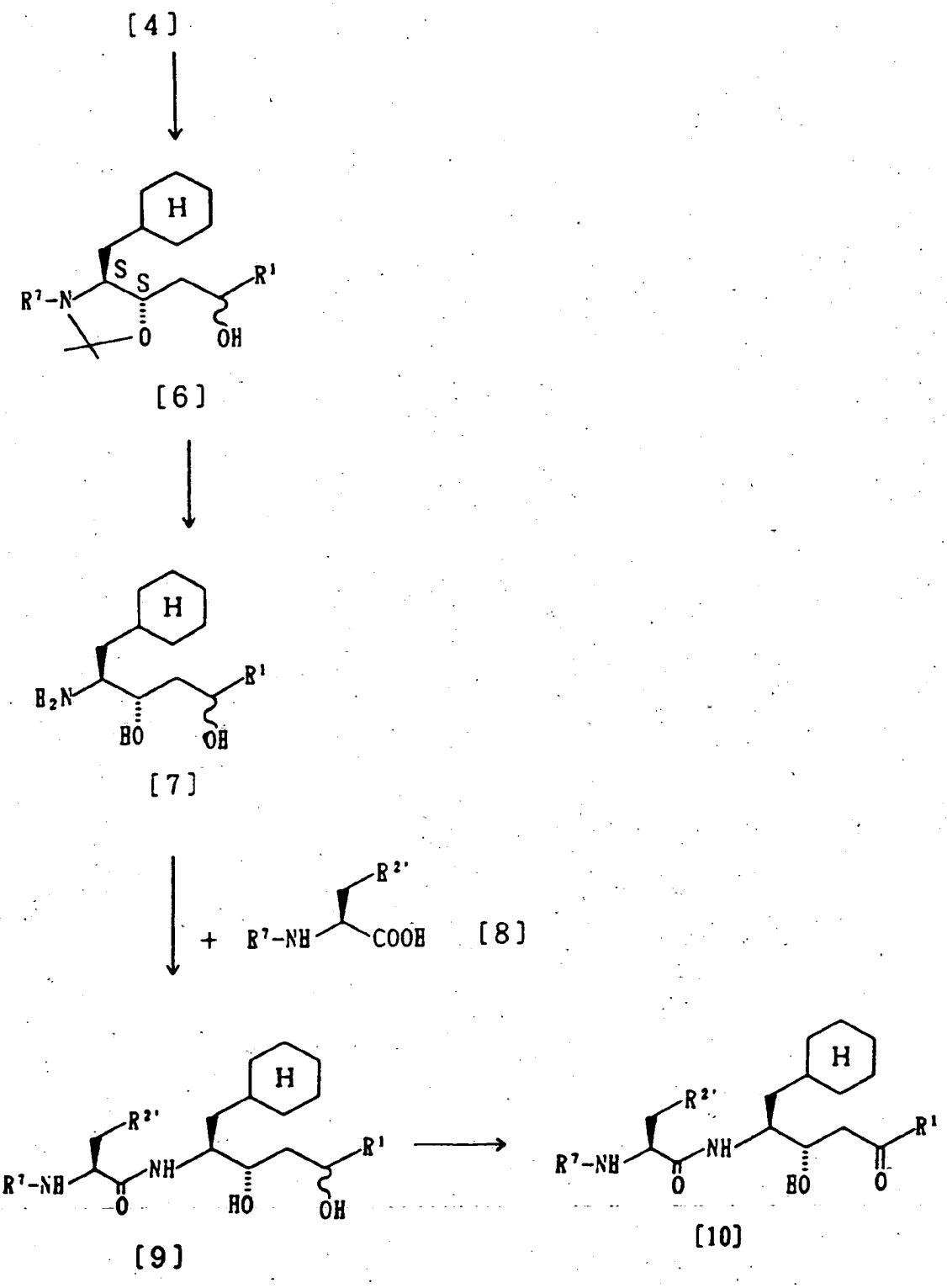


[3]

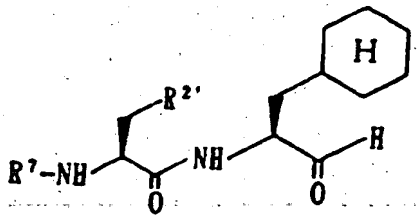


[4] [5]

Step 2a

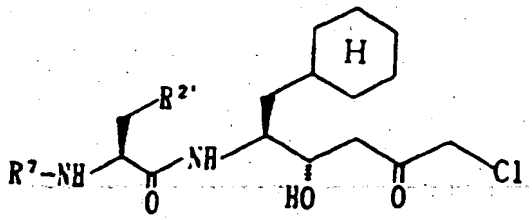

[4]
H
S
S
R¹
R⁷-N
O
OH
[6]
H
H₂N
R¹
HO
OH
[7]
R²'
+ R⁷-NH
COOH
[8]
H
R²'
R⁷-NH
NH
R¹
O
HO
OH
[9]
H
R²'
R⁷-NH
NH
R¹
O
HO
O
[10]

Step 2b

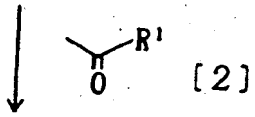


[14]

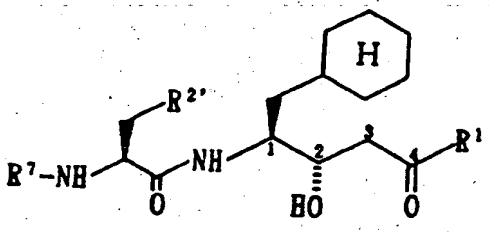
Step 2c



[19]

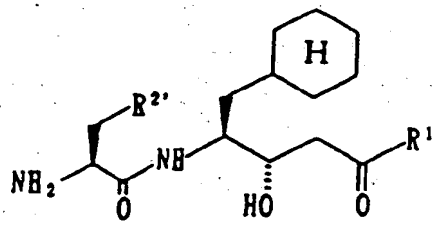


[2]



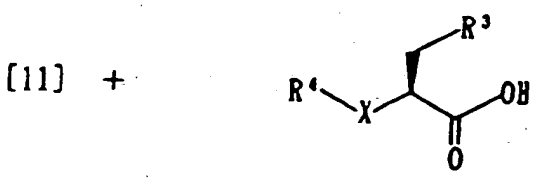
[10]

Step 3

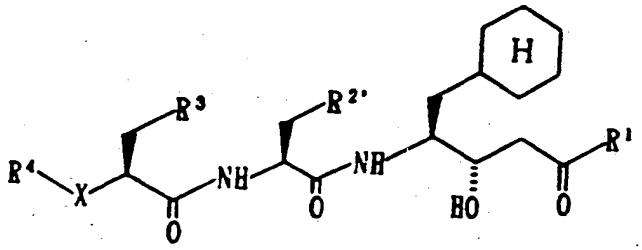


[11]

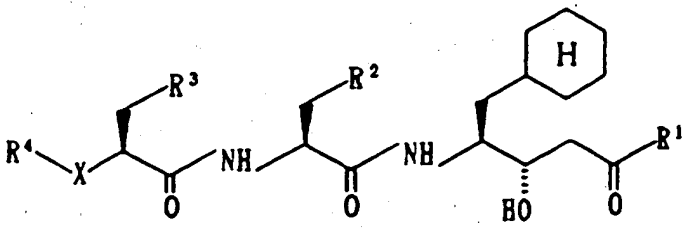
Step 4



[11] + [12] (S)



[13]

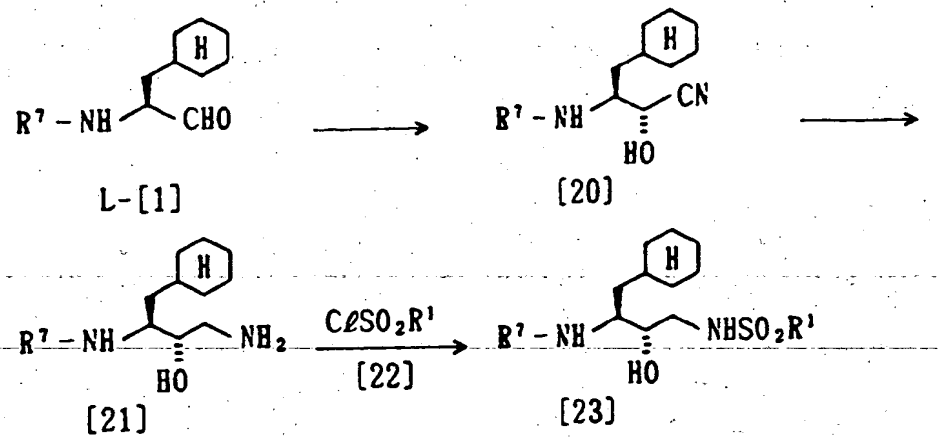


[I A]

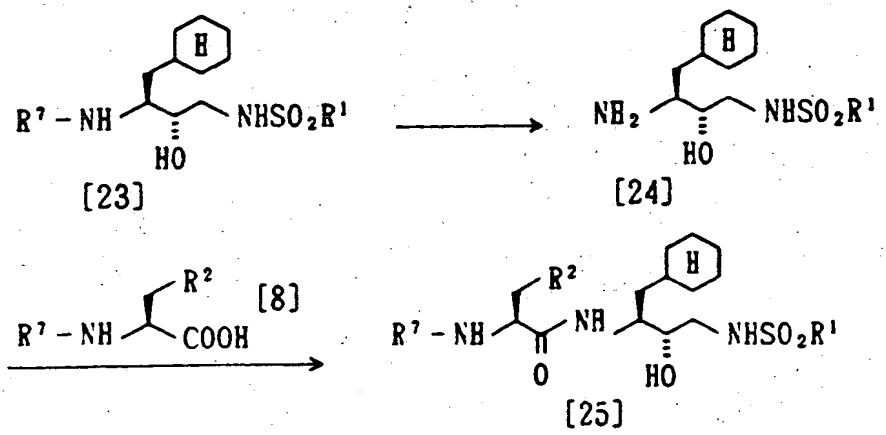
wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1, $R^{2'}$ is protected R^2 and R^7 is an amino protecting group.

4. A process for preparing a compound as defined in Claim 1 or Claim 2 wherein Y is $NHSO_2$ comprising at least the final step of the following reaction scheme:

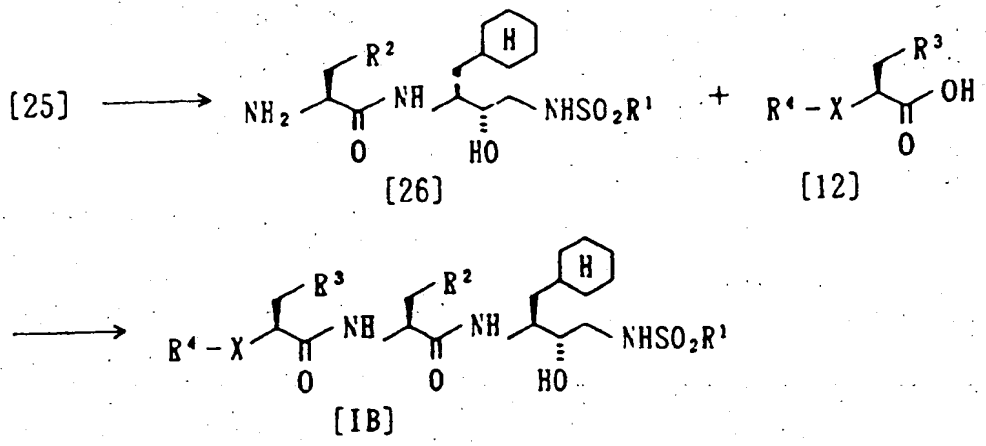
Step 1



Step 2



Step 3



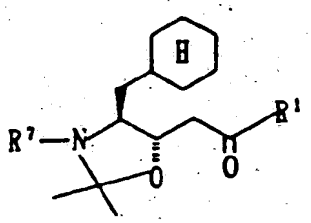
wherein R^1, R^2, R^3, R^4 and X are as defined in Claim 1 and R^7 is an amino protecting group.

5. Th use of a compound as d fined in Claim 1 or Claim 2 in the manufacture of a medicament for use in the tr atment of hypertension.

6. A process for carrying ut a stereo selective aldol condensation between an ald lyde and a ketone wherein the r action is carried out in the presence of a metal amide and a crown ether in an organic solvent and at a temperature in the range -10 to about -100°C.

7. A process as claimed in Claim 8 wherein the amide is sodium bis-trimethylsilylamide ($NaN(TMS)_2$), th crown ether is 15-crown-5 and the temperature is about -78°C.

8. A compound for the manufacture of the derivative of formula (I) of Claim 1, said compound having the formula:



wherein, R^1 is as defined in Claim 1, and R^7 is hydrogen or an amino protecting group.